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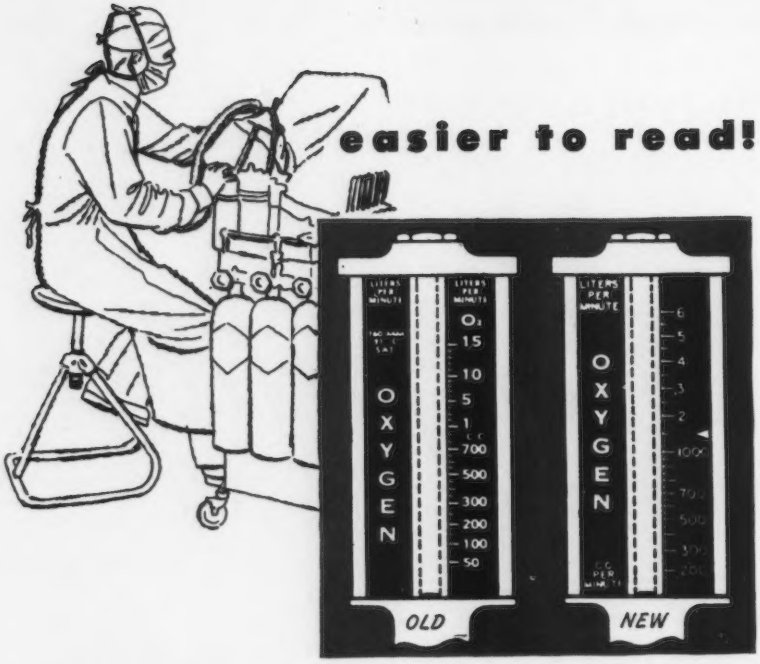

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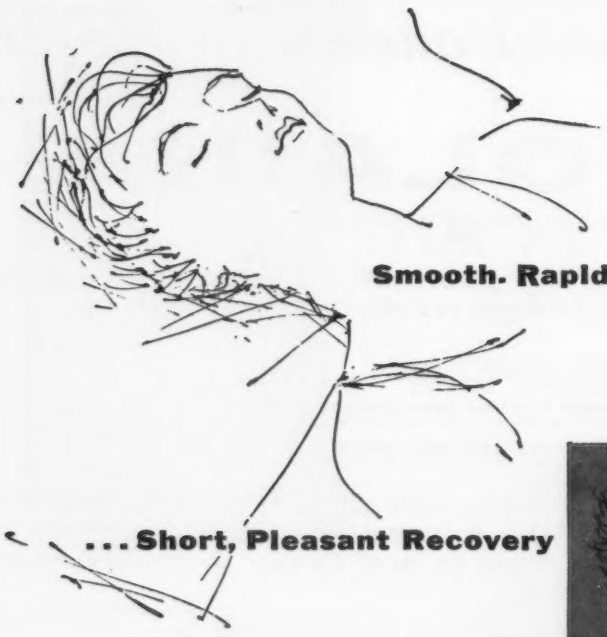

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EDITORIAL

Evaluation of New Drugs in Anaesthesia

With the increasing number of drugs being employed today by anaesthetists, it is important to review briefly some of the problems connected with the proper evaluation or assessment of new agents in this field. By and large, before a new drug reaches the anaesthetist, it has already been submitted to some pharmacological and toxicological investigations on laboratory animals. It must be realized, however, that in most instances such studies are far from complete, and often only of a preliminary nature. The final evaluation of the practical usefulness of a new agent depends primarily upon its efficacy and safety for use in man. Some type of preliminary study along these lines is therefore generally undertaken even before complete laboratory examination is possible. This task is undoubtedly one for the expert anaesthetist and one which entails certain responsibilities. Indeed, the anaesthetist undertaking such an evaluation must not only be an expert in practical anaesthesia, but must also be familiar with the experimental or pharmacological background of the agent. His task, of course, requires some pharmacological know-how. The practical assessment of a new drug is often a difficult and time-consuming job for any anaesthetist. This is much more the case today because of the fact that many anaesthetists employ, justifiably or otherwise, an increasing number of different types of pharmacological agents. Without proper consideration misleading results might be obtained. In order to avoid such pitfalls, the main features of any new drug which should be evaluated as early as possible might be summarized as follows:

1. *Effectiveness or efficacy.* Is the drug really effective for the specific purpose for which it is being studied? Is it superior or inferior to the known agents used for the same purpose? In view of individual differences in susceptibility to drugs, the answers to these questions necessitate careful study of the effects of the agent, in a minimal number of cases, this number of course depending on the scope of usefulness of the drug and various other factors, which it is unneccessary to consider here. It might be emphasized at this point that a critical investigation carried out even with a relatively small number of patients, say ten or twenty, and making a more or less individualized and detailed study in each case, might be the more fruitful approach to the problem. It is preferable to administering the drug routinely to even larger numbers (100 or 200 patients), but doing so with a more superficial and less critical type of study. The available clinical material as well as the actual potency of the drug are of course important considerations in regard to this aspect of drug evaluation.

2. *Safety.* Is the drug free from injurious effects in the body? The answer to this question is not always obvious, and requires keen clinical observations and exact laboratory investigations of the patients, both during the period of drug administration and for some time thereafter. As is well known, several synthetic drugs originally introduced as non-toxic are now known to exert deleterious effects in the body when studied more critically and in larger numbers of patients.

In this connection, therefore, a sufficient number of cases must be studied before a definite conclusion can be drawn. In many instances, the main value of large-scale routine administrations of a new drug is to establish its immediate safety or otherwise in man, rather than to determine either its effectiveness (as referred to above) or its ultimate long-term safety. This is a difficult problem.

3. *Dosage.* The proper dosage of any drug requires careful assessment, and obviously at the start one should administer only small or minimal doses, progressively increasing the amount as the margin of safety of the agent becomes clearer. This is an important and often neglected point; in many instances that margin cannot be assessed by any rule of thumb, but requires careful and well-planned clinical investigation.

4. *Influence of other drugs used in anaesthesia.* The anaesthetist often finds it necessary to use some new agent more or less in place of some other known drug. Obviously, it cannot be assumed that the effects of the new drug, under all conditions, will be identical with those of the old. This is so particularly when it is used in association with other agents, and exact evaluation of the resultant effects, when two or more drugs are administered simultaneously, is difficult and often confusing. In the early stages of the evaluation of new drugs, combination should certainly, therefore, be avoided as far as possible. Unfortunately, there is a strong tendency to believe that "combination" is the same as "potentiation," and caution must be exercised in making drug combinations without clear justification. While there is no doubt that the actions of one drug might be potentiated by the presence of another (positive potentiation or synergism), conversely, the action of one agent might be diminished or antagonized by another (negative potentiation or antagonism), and consequently the anaesthetist is called upon to provide some evaluation of this aspect of the agent under study. This general problem is obviously an important one today in view of the increasing number of drugs being submitted to the anaesthetist for evaluation, and in view of the wide scope of present-day methods into which several "non-anaesthetic" agents and procedures, such as the use of muscle relaxants, of different types of autonomic-blocking vasodepressor drugs, and of hypothermia, etc., have more recently been introduced. These factors impose added tasks and responsibilities in the practical assessment of new drugs in anaesthesia, but are of course more or less unavoidable problems in the search for better and safer methods of anaesthesia, to which Canadian anaesthetists are constantly contributing.

K. I. MELVILLE

EDITORIAL

Evaluation de nouveaux médicaments en anesthésie

Le nombre croissant de médicaments employés aujourd'hui par les anesthésistes nous impose une brève revue de quelques-uns des problèmes qui relèvent de l'évaluation exacte de nouveaux agents dans ce domaine. A tout prendre, avant qu'un nouveau médicament ne parvienne entre les mains de l'anesthésiste, il a été soumis à des essais pharmacologiques et toxicologiques sur des animaux de laboratoire. Il faut savoir cependant que dans la plupart des cas, de telles études sont loin d'être complètes, et sont souvent d'une nature préliminaire. L'évaluation finale de l'utilité pratique d'un nouvel agent dépend principalement de son efficacité et de sa sécurité sur le corps humain. Une étude préliminaire de ce genre est donc faite avant même que l'examen complet en laboratoire soit possible. Cette tâche ressort de l'expert anesthésiste et elle implique certains responsabilités. En effet, l'anesthésiste qui entreprend une telle évaluation doit être non seulement un expert en anesthésie pratique, mais doit aussi avoir une connaissance de l'historique expérimentale ou pharmacologique de l'agent. Sa tâche, il va sans dire, nécessite des connaissances en pharmacologie. L'évaluation pratique d'une nouvelle drogue est souvent un labeur difficile et long pour tout anesthésiste. Cela est d'autant plus le cas aujourd'hui que beaucoup d'anesthésistes se servent à tort ou à raison, d'un nombre croissant d'agents pharmacologiques. Si l'on ne tient pas compte de ce facteur, des résultats erronés peuvent s'ensuivre. Pour éviter de tels dangers, les différents aspects de toute nouvelle drogue à évaluer peuvent être résumés comme suit:

1. *Efficacité.* Le médicament est-il vraiment efficace pour le but précis pour lequel il est étudié ? Est-il supérieur ou inférieur aux autres agents connus servant au même but ? Compte tenu des différences individuelles de susceptibilité aux drogues, les réponses à ces questions nécessitent une étude soignée des effets de l'agent, dans un nombre minime de cas, ce nombre dépendant naturellement de l'étendue de l'utilité de la drogue et d'autres facteurs variés, qu'il n'est pas nécessaire de considérer ici. On pourrait souligner maintenant qu'un examen critique entrepris sur un nombre relativement restreint de patients, disons dix ou vingt, une étude détaillée et plus ou moins individuelle étant faite dans chaque cas, s'offre comme l'approche la plus profitable au problème. Une administration régulière de la drogue à un nombre même plus grand (100 ou 200 patients) est préférable mais cela conduit à une étude plus superficielle et moins critique. Le matériel de clinique disponible, aussi bien que la force actuelle de la drogue sont évidemment des considérations importantes en ce qui concerne cet aspect de l'évaluation d'une drogue.

2. *Sécurité.* La drogue est-elle libre d'effets injurieux sur le corps ? La réponse à cette question n'est pas toujours évidente, et exige du patient les observations cliniques nettes et des études précises en laboratoire pendant la période d'administration de la drogue et dans les jours qui suivent. Il est de fait courant que plusieurs drogues synthétiques, d'abord introduites comme non-toxiques, ont

révélé par la suite des effets nuisibles sur l'organisme, lorsqu'elles ont été étudiées d'une façon plus critique et sur un nombre plus étendu de patients. Un nombre suffisant doit donc être étudié avant de déduire une conclusion définie. Dans bien des cas, la valeur principale des administrations régulières d'une nouvelle drogue, est d'établir la sécurité immédiate de son emploi chez l'homme, plutôt que de déterminer ou son efficacité (tel qu'indiqué ci-dessus) ou la sécurité à longue échéance de son emploi. Violà la difficulté du problème.

3. *Dosage.* Le dosage exact de tout médicament exige une évaluation soignée et il est évident qu'au début, on doit administrer de petites ou des doses minimes, en augmentant progressivement la quantité à mesure que la marge de sécurité de l'agent se précise davantage. C'est là un point important et souvent négligé; dans bien des cas cette marge de sécurité ne peut pas être déterminée par une méthode empirique, mais nécessite en clinique, une étude soignée et bien organisée.

4. *Influence d'autres médicaments employés en anesthésie.* L'anesthésiste doit souvent employer un nouvel agent pour remplacer plus ou moins une autre drogue connue. Il est évident qu'on ne peut pas assumer que les effets de la nouvelle drogue seront identiques à l'ancienne, toute chose étant égale. Ceci est particulièrement le cas lorsqu'elle est employée en association avec d'autres agents, et l'évaluation exacte des effets qui en résulte est difficile et souvent confuse, lorsque deux drogues ou plus sont administrées simultanément. Dans les premières étapes de l'évaluation de nouvelles drogues, on doit donc éviter les combinaisons autant que possible. Malheureusement, il y a une tendance forte à croire que « combinaison » est synonyme de « potentialisation » et l'on doit procéder avec précaution lorsqu'on opère des combinaisons de drogues, sans justification déterminée. Quoiqu'il n'y ait aucun doute que les actions d'une drogue peuvent être augmentées par la présence d'une autre drogue (potentialisation positive ou synergique) et ceci réciproquement; l'action d'un nouvel agent peut être affaiblie ou neutralisée par une autre (potentialisation négative ou antagoniste) et par conséquent l'anesthésiste est appelé à fournir une évaluation de cet aspect de l'agent étudié. Ce problème général est évidemment important aujourd'hui, compte-tenu du nombre croissant de drogues soumises à l'anesthésiste aux fins d'évaluation, et considérant la vaste étendue des méthodes employées aujourd'hui où entrent plusieurs agents ou procédures non-anesthésiques, tels l'emploi de relaxants musculaires, et différents types de drogues de blocage autonomiques, vaso–dépresseurs et hypothermiques, etc. Ces facteurs imposent des tâches et des responsabilités nouvelles pour l'évaluation pratique de nouvelles drogues en anesthésie, mais constituent naturellement des problèmes qui peuvent être plus ou moins évités dans la recherche de méthodes meilleures et plus sûres en anesthésie, une recherche à laquelle contribuent sans cesse les anesthésistes canadiens.

K. I. MELVILLE

INVESTIGATION OF NEW DRUGS, WITH SPECIAL REFERENCE TO LARGACTIL (CHLORPROMAZINE, THORAZINE R.P. 4560, M & B 2378, 2601A S.K.F.) AS AN EXAMPLE*

R. G. B. GILBERT, M.D., F.R.C.P.(C), D.A., ALLAN B. DOBKIN, M.D., and LOUIS LAMOUREUX, M.D.**

MANY anaesthetists, including one of the authors (1) have been advocating, if not a return to simpler forms of anaesthetic procedure, then the use of techniques and drugs with care and thought concerning morbidity. A timely comment, such as that written by Dr. Langton Hewer entitled "Whither Anaesthesia" (2), should lead to caution being exercised by the more rabid members of our specialty.

How can such views be reconciled with those expressed by many, that modern anaesthesia is an aid to modern major surgery, without which many operations could not be performed? The answer is, of course, that progress can be made with the maintenance of conservative thought and by carrying out research along fairly well formed, traditional lines.

New techniques, drugs, and ideas come and go. They may even be rediscovered; in this connection Gillespie (3) has reminded us of Bernard Shaw's *Doctor's Dilemma*. Eventually, however, with the appreciation of merit, such innovations find their own level. Once accepted, they are assigned the time-honoured qualifications: indications, contraindications and complications.

Such concepts have governed investigations recently reported from our Department (4, 5, 6, 7).

When a group of new drugs or a new member of a group is presented to our specialty, should it be accepted as advertised and used on the evidence of clinical impression? Some may, if extensive clinical trial and laboratory research by others warrant it. In this case they should be introduced with caution and in the presence of available knowledge to compete with complications.

What happens if a panacea be grasped without fair trial? An example may be given in the use of Efocaine, following which serious complications, the possibility of which were at first denied, have occurred (8, 9).

What is desired of a New Drug?

1. A new drug must have a desirable specific action. It should not be assessed according to its portion in a cocktail (10).
2. It must be of low toxicity.
3. It must possess controllability and reversability.
4. It must present few complications.
5. It must be possible to deal rationally and easily with such complications.

*Presented at the Annual Meeting, Canadian Anaesthetists' Society, Vancouver, British Columbia, June 14–15, 1954.

**From Queen Mary Veterans' Hospital, Montreal, McGill University and Université de Montréal.

If these conditions are fulfilled, then it must be proven that the new drug is at least as good as, if not superior to, any pre-existing counterparts. To these conditions should be added, ease of production and cost. In the words of Dr. Harold Griffith when discussing relaxant drugs, "D-Tubo Curare will not be replaced until something better can be discovered, then given full and satisfactory clinical trial."

Investigations

Drugs may be investigated in a number of ways; in anaesthesia relatively accurate data can be obtained.

The agents can be given to a normal volunteer, once they have passed the animal stage. They can then be given clinical trial and used in pathological states.

Animal experimentation yields much information but accurate inferences cannot always be made owing to differences between species.

From combined evidence, so deduced, the mode of action of the drug is sought; likewise it is evaluated.

Figure 1

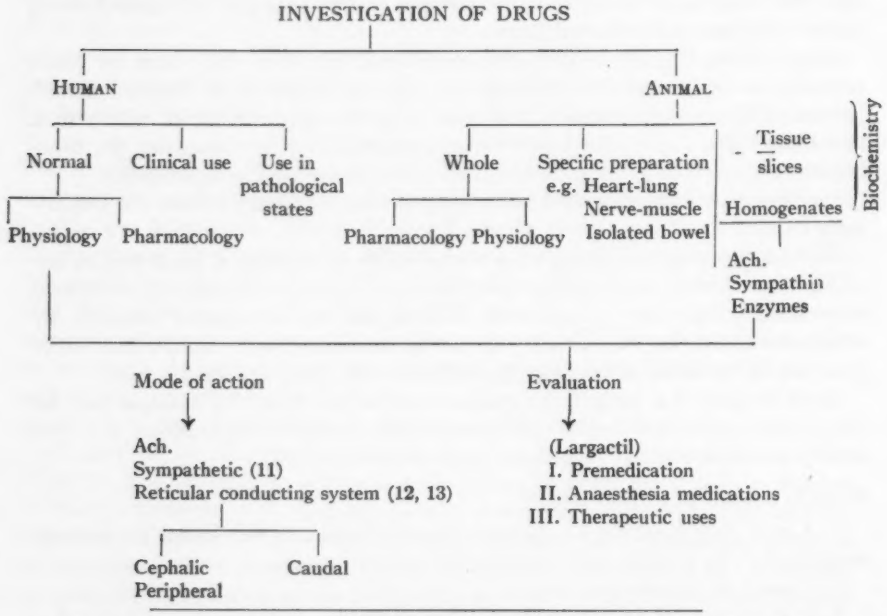


Figure 2 is an endeavour to illustrate some of the observations and investigations which can readily be carried out. They can be divided into those affecting the cardiovascular system, the respiratory system, and so forth.

The action of the greatest proportion of the drugs which are used in anaesthesia is mediated by the nervous system. Therefore special note must be made of the effects of the drug upon it.

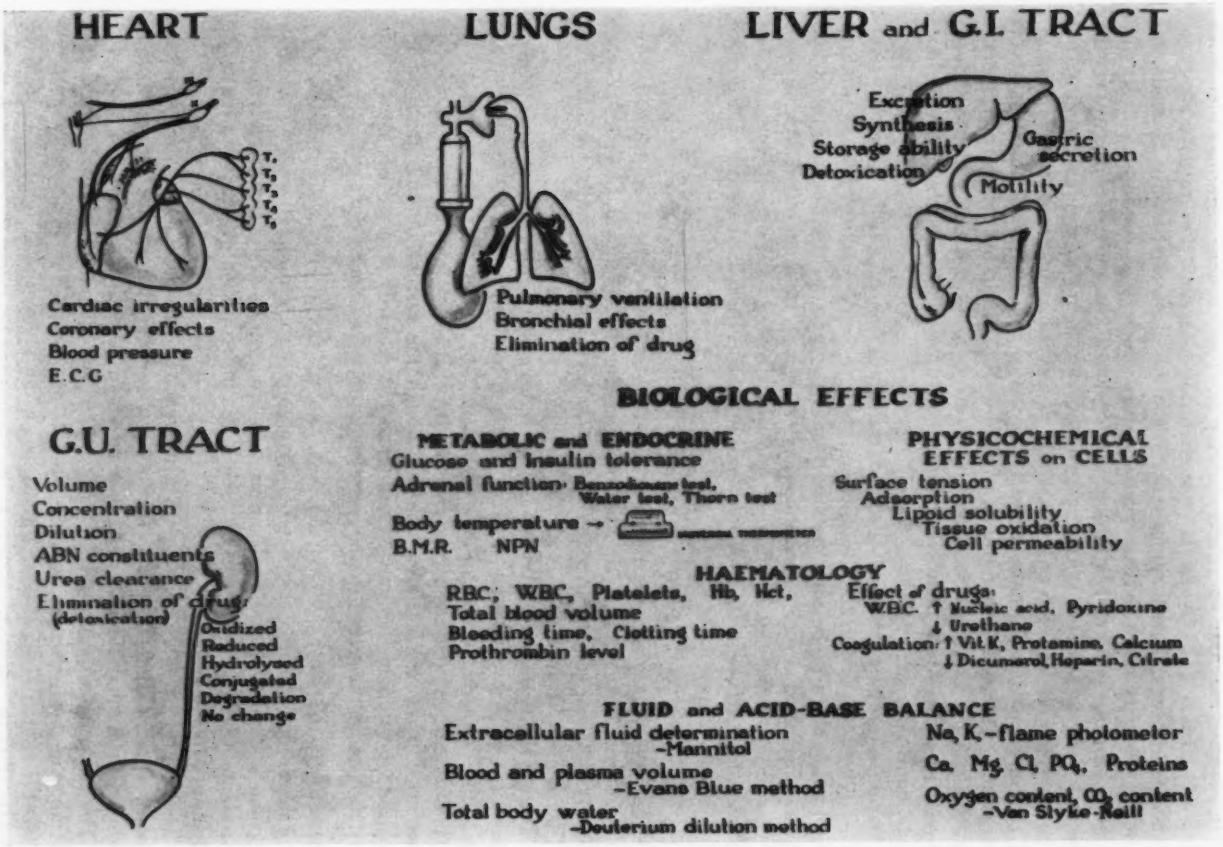

HEART
LUNGS
LIVER and G.I. TRACT
Cardiac irregularities
Coronary effects
Blood pressure
E.C.G
Pulmonary ventilation
Bronchial effects
Elimination of drug
Excretion
Synthesis
Storage ability
Detoxication
Gastric secretion
Motility
BIOLOGICAL EFFECTS
G.U. TRACT
Volume
Concentration
Dilution
ABN constituents
Urea clearance
Elimination of drug:
(detoxication)
Oxidized
Reduced
Hydrolysed
Conjugated
Degradation
No change
METABOLIC and ENDOCRINE
Glucose and Insulin tolerance
Adrenal function: Benzodioxane test, Water test, Thorn test
Body temperature →
B.M.R. NPN
PHYSICOCHEMICAL EFFECTS on CELLS
Surface tension
Adsorption
Lipoid solubility
Tissue oxidation
Cell permeability
HAEMATOLOGY
RBC; WBC, Platelets, Hb, Hct,
Total blood volume
Bleeding time, Clotting time
Prothrombin level
Effect of drugs:
WBC. ↑ Nucleic acid, Pyridoxine
↓ Urethane
Coagulation: ↑ Vit K, Protamine, Calcium
↓ Dicumerol, Heparin, Citrate
FLUID and ACID-BASE BALANCE
Extracellular fluid determination
-Mannitol
Blood and plasma volume
-Evans Blue method
Total body water
-Deuterium dilution method
Na, K, -flame photometer
Ca, Mg, Cl, PO4, Proteins
Oxygen content, CO2 content
-Van Slyke-Neill

FIGURE 2

In Figure 3 may be seen charts of Paton (14) concerning neuromuscular block and of Adriani (15) when he systematically describes the pharmacology of anaesthetic drugs. This diagram emphasizes the close relationship between our clinical specialty and the basic sciences upon which it is based.

In a previous paragraph attention was drawn to the action of drugs upon the central nervous system. With the growing development and use of blocking agents which act at different levels, study of this action becomes more important, if the anaesthetist is to have at least a working knowledge of the drugs at his command. Figure 4 is an attempt to show the possible effects upon specific portions of the nervous system and to give examples of drugs which call forth such a response. More detailed nervous structures and conducting systems have been omitted.

While a drug is being studied, specific pathological effects must be given constant observation. Is that drug irritant, when taken by mouth? Does it produce thrombosis when given intravenously? Does it give rise to tissue necrosis when given intramuscularly or subcutaneously? What is its minimal lethal dose? Figure 5 classifies some of the possible complications which may be anticipated. Consideration must be given to all of these and more besides before a satisfactory review can be made.

Largactil

The Department of Anaesthesia at Queen Mary Veterans' Hospital, aided by a Fellow in Anaesthesia, Dr. Allan B. Dobkin, and many of the resources at that Institution, has recently undertaken studies with Largactil. These studies have been published elsewhere (5).

During the work, some systems proved more easy of investigation than others, and were at the same time of great importance. Hence, much time was spent on the respiratory system and on metabolism. One reason for this was the report that Largactil stimulated respiration, this being a deduction from animal experimentation. Our results showed that although the respiration rate may be increased, the minute volume is considerably decreased. It was also shown that metabolism, as measured by oxygen consumption, was not depressed.

Sympathetic Nervous System

Early in our studies, which actually commenced with hypothermia in view, it became evident that the hypothermia was brought about by marked peripheral vasodilatation. This fact has been used in the investigation of peripheral vascular disease (6).

Temperature studies, made with a universal thermometer, carrying ten electrodes, showed that Largactil produces a peripheral response equal to that induced by lumbar sympathetic block or spinal anaesthesia.

The importance of the use of Largactil in this field for both diagnostic and therapeutic purposes may be considered.

That Largactil is a potent depressor of the sympathetic nervous system is proven, though the actual site of the depression is open to debate. Another factor in this connection is the pin point pupil which may be noted following the use of Largactil. This may be equal in calibre to that produced by Morphine.

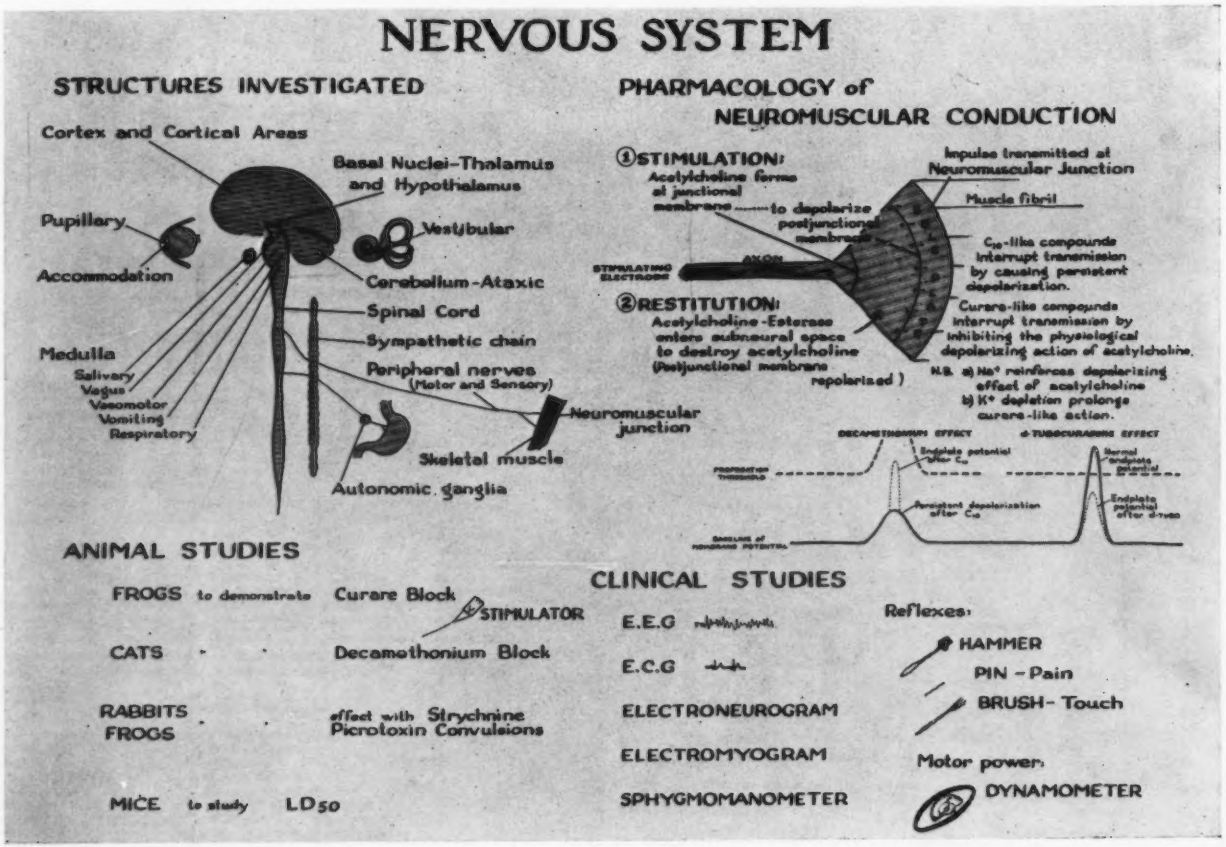

NERVOUS SYSTEM
STRUCTURES INVESTIGATED
Cortex and Cortical Areas
Basal Nuclei-Thalamus and Hypothalamus
Pupillary
Vestibular
Accommodation
Cerebellum-Ataxic
Spinal Cord
Sympathetic chain
Medulla
Peripheral nerves (Motor and Sensory)
Salivary
Vagus
Vasomotor
Vomiting
Respiratory
Neuromuscular junction
Skeletal muscle
Autonomic ganglia
PHARMACOLOGY of NEUROMUSCULAR CONDUCTION
①STIMULATION:
Acetylcholine forms at junctional membrane ..... to depolarize postjunctional membrane
Impulse transmitted at Neuromuscular Junction
Muscle fibril
STIMULATING ELECTRODE
AXON
②RESTITUTION:
Acetylcholine-Esterase enters subneural space to destroy acetylcholine
(Postjunctional membrane repolarised)
C10-like compounds interrupt transmission by causing persistent depolarization.
Curare-like compounds interrupt transmission by inhibiting the physiological depolarizing action of acetylcholine.
N.B. a) Na+ reinforces depolarizing effect of acetylcholine
b) K+ depletion prolongs curare-like action.
DECAMETHONIUM EFFECT
d-TUBOCURARINE EFFECT
Endplate potential after C10
Normal endplate potential
PROPAGATED THRESHOLD
Persistent depolarization after C10
Endplate potential after d-tubo
RECOVERY OF MEMBRANE POTENTIAL
ANIMAL STUDIES
FROGS to demonstrate Curare Block
STIMULATOR
CATS
Decamethonium Block
RABBITS
FROGS
effect with Strychnine Picrotoxin Convulsions
MICE to study LD50
CLINICAL STUDIES
E.E.G
E.C.G
ELECTRONEUROGRAM
ELECTROMYOGRAM
SPHYGMOMANOMETER
Reflexes:
HAMMER
PIN - Pain
BRUSH - Touch
Motor power:
DYNAMOMETER

FIGURE 3

FIGURE 4: DRUGS AFFECTING NEUROMUSCULAR SYSTEM

CORTEX NUCLEI MEDULLA

STIMULANT	PICROTOXIN METRAZOL AMPHETAMINE
DEPRESSANT	BARBITURATES BROMIDES CHLORAL
ANALGESIC	MORPHINE DEMEROL METHADON
ANESTHETIC	ETHER CYCLOPROPANE
ANTICONVULSANT	MESANTOIN TRIDIONE
EMETIC	APOMORPHINE
ANTIEMETIC	LARGACTIL DRAMAMINE
ANTIATAXIC	DRAMAMINE LARGACTIL

AUTONOMIC NERVOUS SYSTEM

EXCITORS

INHIBIT MEDIATOR-DESTROYING ENZYMES (ANTICHOLINESTERASE)

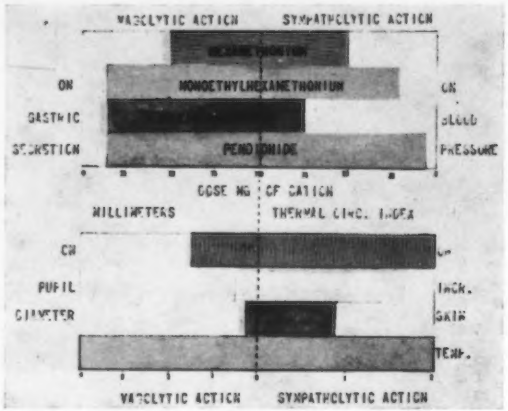
PARASYMPATHO.	SYMPATHO.
PHYSOSTIGMINE	EPHEDRINE
PROSTIGMINE	
TENSILON	
DFP	

SUPPORT NORMAL MEDIATOR (ACETYLCHOLINE) ACTS DIRECTLY ON INNERVATED STRUCTURE

GANGLIONIC	PARASYMPATHO.	SYMPATHO.
ACETYLCHOLINE	URECHOLINE	NOREPINEPHRINE
NICOTINE	PILOCARPINE	EPINEPHRINE
NECHOLYL	ARECOLINE	NEOSYNEPHRINE
CARRACHOL		ISUPREL
		METHEDRINE
		VASOXYL
		WYAMINE

DEPRESSORS

GANGLIONIC	ANTICHOLINERGIC	ANTIADRENERGIC
TETRAETHYLAMMONIUM	ATROPINE	ERGOTOXINE
PENTAMETHONIUM	SCOPOLAMINE	BENZODIOXANE
HEXAMETHONIUM	COCAINE	DIBENAMINE
PENDIOMIDE		PRISCOLINE
ARFONAD		
APRESOLINE		
TUBOCURARINE		
FLAXEDIL		



PERIPHERAL NERVOUS SYSTEM

A. DEPRESS SPINAL CORD

MEPHENESIN
PRENDEROL
BENZIMIDAZOLE

B. DEPRESS NERVE TRUNKS

PROCAINE NUPERCAINE
METYCAINE XYLOCAINE
PONTOCAINE CYCLAINE

C. DEPRESS MYONEURAL JUNCTION

I COMPETE WITH ACETYLCHOLINE FOR RECEPTOR

TUBOCURARINE
METUBINE
FLAXEDIL
MYTOLON
DIHYDROERYTHROIDINE

II DEPOLARIZATION OF RECEPTOR MEMBRANE

NICOTINE	SUCCINYLCHOLINE
ACETYLCHOLINE EXCESS	PENDIOMIDE
TEA c5 c6 c10	ARFONAD

III INTERFERE WITH RELEASE OF ACETYLCHOLINE?

PROCAINE
PROBANTHINE
LARGACTIL

D. DEPRESS SMOOTH MUSCLE

PAPAVERINE
NITRITES
XANTHINES
NICOTINIC ACID
HISTAMINE

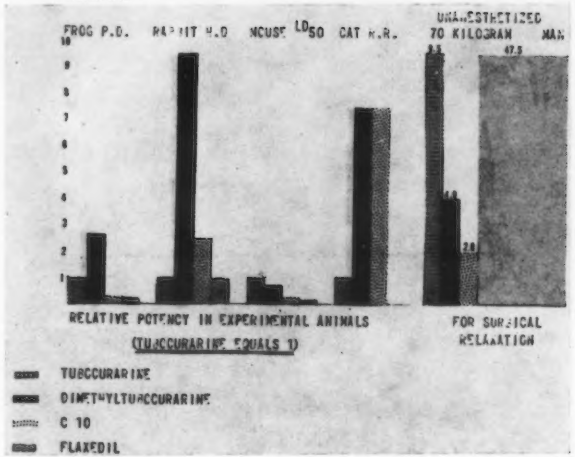


FIGURE 5

PATHOLOGICAL EFFECTS OF ANAESTHETIC DRUGS

SITE	ETIOLOGY	EFFECT
BRAIN	TOXICITY HYPOTENSION ANOXIA ISCHAEMIA	CONVULSIONS MENTAL IMPAIRMENT
HEART	TOXICITY HYPOTENSION ANOXIA REFLEX ISCHAEMIA	ARRHYTHMIA FIBRILLATION BLOCK CONGESTIVE FAILURE INFARCTION THROMBOEMBOLISM
LUNG	ALLERGY (HISTAMINE) OBSTRUCTION ASPIRATION	BRONCHOSPASM ATELECTASIS EDEMA PNEUMONITIS
LIVER	HYPOTENSION (HEMORRHAGE) ANOXIA TOXICITY	SHOCK (HEPATITIS) NECROSIS
KIDNEY	HYPOTENSION ANOXIA TOXICITY TRANSFUSION REACTION	GLOMERULONEPHRITIS LOWER NEPHRON BLOCK
NERVE MUSCLE	FAULTY POSTURING TOXICITY	PARESIS
TARGET ORGAN	SURGERY SEPSIS	TRAUMA INFECTION

Parasympathetic Nervous System

Largactil has been stated to be vagolytic. In some respects it may be, but in others it is not.

Gastric secretions were shown to be much diminished after Largactil but following the use of insulin there is a rise in gastric secretion and blood sugar. This suggested that there was no vagal block to gastric secretion.

Premedication

The data of Cohen and Beecher (16) were used in the assay of the use of Largactil for premedication. The clinical results of our studies have already been published (5). They suggested important features to be gained, under many circumstances, prior to operation, during operation, and following it.

These results have since been co-ordinated with experimental work, carried out with the invaluable aid of Dr. K. I. Melville (7). The main objects of this

were to follow the responses of vasopressors after the use of Largactil, to investigate the reversal effect of the action of adrenalin, and to assess the ability of Largactil to protect the mechanism of the heart action, under a variety of circumstances.

Summary

Suggestions concerning the investigation of drugs by a department of anaesthesia have been made.

Claims (17, 18, 19, 20, 21, 22, 23) of a relatively new phenothiazine derivative, Largactil, have in some ways been substantiated, in others modified.

It is hoped that the pre-existing clinical data (24, 25, 26) have been augmented.

Résumé

Beaucoup d'anesthésistes préconisent l'emploi avec soin et considération de médicaments et de techniques anesthésiques nouvelles en ce qui concerne la morbidité. Des progrès peuvent être faits par le maintien de vues prudentes et la conduite dans la recherche doit suivre des lignes traditionnelles bien établies. Des techniques, des drogues et des idées nouvelles se présentent et disparaissent. Ces innovations, à la longue, trouvent leur juste niveau d'utilité. Une nouvelle drogue, si elle est utile, doit avoir une action précise et voulue, une faible toxicité, doit être maniable et reversible, elle doit présenter peu de complications et on doit les pouvoir résoudre facilement et d'une manière rationnelle. Ayant satisfait ces critères la nouvelle drogue doit être au moins aussi bonne que ses contreparties existantes.

L'action de la nouvelle drogue doit être étudiée d'abord sur des animaux, et plus tard avec prudence sur des sujets humains. Son action précise sur le fonctionnement des différents organes et systèmes du corps humain doit être soigneusement évaluée. Les effets pathologiques doivent être observés avec soin.

Les auteurs ont entrepris l'étude du Largactil suivant les bases indiquées. Ils ont montré que la fréquence des mouvements respiratoires peut être accélérée mais le volume par minute est considérablement diminué. On a aussi trouvé que le métabolisme, étant mesuré par la consommation d'oxygène, n'a pas été déprimé. On a établi que le Largactil est un puissant abaisseur du système sympathique nerveux, et qu'il produit une dilatation vasculaire périphérique égale à celle produite par le bloc lombaire sympathique ou anesthésie lombaire. Les auteurs n'ont pas pu démontrer une action vagolythique imputable à la drogue mais sa valeur comme agent de prémédication avant l'opération a été établie.

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CLINICAL IMPRESSIONS ON THE USE OF LARGACTIL AT SHAUGHNESSY HOSPITAL*

R. E. SIMPSON, M.D.**

THE term "artificial hibernation" first aroused our interest in Largactil. Huguenard (2) produces a state of "artifical hibernation," which has many of the characteristics of true hibernation, by means of a diffuse blockade of the whole autonomic nervous system, peripherally, at the synapses, and centrally. Thus the patient, his autonomic system unable to respond to injury, would be protected from shock produced by his own defence reactions.

This state is achieved by the use of the now well-known "Lytic cocktail," in which Huguenard combines a dozen or more "lytic" drugs. The Phenothiazine derivatives, Phenergan, Diparcol, and Largactil, however, are the main constituents of this cocktail. Their effects are essentially similar, but Huguenard considers Largactil as the most important single agent in his technique.

The chemical, physical, and pharmacological properties of Largactil have been most adequately described in the literature so only a brief résumé of its effects as related to anaesthesia will be considered.

Largactil has depressant action on the central nervous system which has not yet been completely defined. This depressant activity produces in many subjects a state of disinterestedness, sometimes described as a pharmacodynamic lobotomy. Reduced metabolism, hypothermia, absence of central vomiting, antagonism to central nervous system stimulants, and enhancement of the action of general anaesthetics, hypnotics, and analgesics are also reflections of this central depression.

Largactil not only produces muscle relaxation by a central action similar to that of myanesin, but also enhances the effect of Flaxedil, which acts peripherally.

This drug is an active adrenergic blocking agent. Parasympathetic functions, on the other hand, are inhibited only by larger doses of Largactil. Laboratory experiments show that, as well as exerting some protective action on haemorrhagic and traumatic shock, the compound has a definite stabilizing effect on adrenalin-induced cardiac arrhythmias.

Finally it should be noted that the drug is very irritant to tissues. Apparently this property depends on the concentration of the drug and not its low pH (5.3–5.6), and it is recommended that the drug be given deeply intramuscularly or diluted when given intravenously.

Largactil has now been used in Shaughnessy Hospital in a total of 330 male patients.

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LARGACTIL ADMINISTRATION—330 CASES

Total no.—Premedications (oral & I.M.)	246
Total no.—I.V. in O.R.	84
	330
Average age of patients	64.6 yrs.
Average weight of patients	146 lbs.

These figures illustrate the operations and field covered:

TABLE I

	Oral	Intramuscular	Intravenous	Total
General anaesthetics	30	66	44	140
Spinal	80	55	30	165
Blocks	10	5	10	25
Total	120	126	84	330

General Surgery	171
Orthopaedics	58
Genito-urinary	50
Chest	25
Plastic	17
Neurosurgery	7
E.N.T.	2
Total	330

It was decided to combine Largactil with our usual techniques modifying them as little as possible. Usual premedication was not reduced and the clinical condition of the patient determined entirely the types and amounts of agents used.

The drug was first used intravenously during surgery, and later orally and intramuscularly in conjunction with normal premedication.

Intravenous Use of Largactil

Largactil was used intravenously in a total of 84 cases. The drug was usually mixed with 500 cc. of Code 8, at first in 100 mgm. doses but later 50 mgm. were considered sufficient. In many cases this method was not satisfactory, mainly because the prolonged action of the drug made the depth of anaesthesia difficult to assess. The patient would arrive in the post-anaesthetic recovery room depressed and considerable extra care was necessary. Respiratory obstruction was a common difficulty; patients, although easily aroused by shaking, would lapse into a flaccid semi-comatose state, the tongue blocking the airway.

In some cases, however, anaesthesia was smooth throughout, and the post-

operative period uneventful. These patients, usually in the older age group, required small amounts of anaesthetic agents and seemed to make an unusually good recovery.

A number of patients under spinal anaesthesia, who exhibited nervousness, were given Largactil into the intravenous drip. Doses as small as 5 mgm. often produced a very satisfactory sedation for the length of the procedure. Although the B.P. usually remains unchanged, and no marked drops were noted, Largactil should be used cautiously with spinal anaesthesia.

Other observations may be listed as follows:

1. Intravenous administration usually took 5 minutes to become effective, and maximum effects did not occur for 20 to 25 minutes.

2. The skin was warm and dry and the facies pale. Occasionally a rather marked pallor was observed.

3. Redness at the site of injection was noted in only four cases, and was transitory in nature. No cases of thrombophlebitis were discovered during the post-operative follow-up.

4. Four patients under general anaesthesia had a Cheyne-Stokes pattern of breathing throughout part of the procedure. Breathing, however, was usually deep and sometimes more rapid than usual. Rates as high as 30–40 per minute have been observed—usually concomitant with light N_2O anesthesia.

5. A marked fall in B.P. occurred in 15 patients, all of whom were over 40 and most in the 60–80 age group. These cases were treated by posture, oxygen, and the intravenous administration of vasopressors in fairly large doses. B.P. usually rose transiently and further doses were often required. Doses of 2 and even 4 mgm. of Neosynephrine sometimes failed to raise the B.P. to preoperative levels.

The following case is of interest:

Mr. A. R., a 49-year-old man in good physical health with a diagnosis of cortical atrophy.

The patient was booked for a pneumo-encephalogram. This was one of our early cases and chosen deliberately although it was expected that the erect posture might not be well tolerated.

Normal B.P. was 105/90. He received the usual premedication of 100 mgm. of Demerol and 1/150 of Hyoscine, and arrived in the operating room completely aware and only moderately well sedated. Largactil 50 mgm. in 500 cc. of Code 8 was administered intravenously during the hour immediately prior to operation. 25 mgm. of Demerol was given into this intravenous. The patient gradually became very sleepy with deep, slow respiration. Pulse rose from 100 to 120, and the B.P. dropped to 90/70. In the sitting position the systolic pressure dropped to 40 mm. of Hg. and soon became imperceptible, necessitating a rapid change to the Trendelenburg position. 30 mgm. of Methedrine intravenously raised the systolic B.P. to 70 and an additional 30 raised it to 110, but it dropped again to 60 mm. in the upright position. The procedure was then completed with the patient receiving only oxygen by mask.

B.P. remained at 90/60 in the X-ray room where a further 30 mgm. of Methedrine produced no change.

This patient was still semi-comatose when sent to the post-anaesthetic recovery room from X-ray. He did not retch or vomit and his skin was warm and dry in marked contrast to the usual sweating seen in these cases.

It was 5 P.M., eight hours after the anaesthetic, when this patient first became aware, although he responded to painful stimuli long before.

Four characteristics of Largactil are dramatically illustrated in this case:

1. The adrenergic blockade and its associated orthostatic hypotension. The sympathomimetic effects of Methedrine were greatly reduced, if not blocked entirely.
2. The antagonism to analeptics, in this case Methedrine.
3. The enhancement or potentiation of opiates, e.g. Demerol.
4. The abolition of the nausea and vomiting commonly seen after pneumoencephalogram.

Intramuscular and Oral Use of Largactil

Largactil was used as an adjunct to premedication both orally and intramuscularly. Premedications were not reduced, Largactil merely being used in place of Nembutal or Seconal 1½ hours preoperatively in the case of oral doses, or 1 hour preoperatively when the intramuscular route was used.

Doses varied from 12.5 mgm. to 125 mgm., no doses over 50 mgm. being given intramuscularly. Many of these patients came to surgery with excellent sedation, often disinterested in their surroundings and apparently asleep. They could be easily roused, however, and would respond intelligently to questions. No patient showed the hyper-excited or confused state sometimes seen with barbiturates. Approximately half of our patients were inadequately premedicated, some volunteering the information that their premedication for previous operations had been more satisfactory.

Fifteen patients received 100 mgm. or more of oral Largactil. Of these only three were adequately sedated. One, on the other hand, was so deeply depressed that his operation was delayed for approximately two hours. This was the only patient in our series where premedication interfered with surgery. Four patients in this group were nauseated, and one actually retched. Seven patients were nervous and jumpy, four of these being extremely apprehensive.

As a whole, intramuscular injections were more satisfactory. More patients were adequately sedated, and restlessness or nausea has not been recorded.

TABLE II

	Largactil 25 mgm. I.M.		Controls	
	Operative time	Blood loss	Operative time	Blood loss
Lobectomies—13 cases	2 hr. 30 min.	813 cc.	2 hr. 50 min.	1250 cc.
1st stage thoracoplasties—4 cases	1 hr. 30 min.	925 cc.	1 hr. 30 min.	850 cc.
2nd stage thoracoplasties—4 cases	1 hr.	842 cc.	1 hr. 15 min.	925 cc.
Pneumonectomies—1 case	2 hr. 30 min.	1889 cc.	2 hr. 25 min.	1485 cc.

Twenty-two chest patients in which blood loss was measured were given Largactil 25 mgm. in addition to their premedications. These were compared with 22 control patients. Average blood pressure levels in the Largactil group were approximately the same as in the controls.

No significant difference in blood loss is found in this small series.

In both the oral and intramuscular groups, eight patients showed moderately severe blood pressure drops which were unresponsive to ordinary doses of vasopressors. These patients were either given larger doses of vasopressors or carried status quo—if their condition warranted.

Largactil does appear to have some *advantages*:

1. Our general clinical impression was that the amounts of anaesthetic agents can be reduced. This was not true of all cases, but certain patients, particularly in the older age groups, have been maintained for long periods on a 3–1 mixture of N_2O–O_2 after Largactil premedication and small doses of Pentothal and Curare for induction.

2. It was hoped to show a decrease in the amount of postoperative narcotics used. This was the initial impression, but after more critical analyses, no significant reduction was noted.

3. Largactil appears to be a powerful anti-emetic. However, owing to the low incidence of postoperative vomiting in this hospital, and the limited number of cases studied, we have had little experience with Largactil in this respect.

4. The operative and postoperative courses are often unusually smooth, especially in the aged.

5. Largactil has proved of some use in sedating the postoperative excitement such as that seen after cyclopropane anaesthesia.

Its *disadvantages*, however, appear to outweigh the advantages:

1. The drug is very irritant and must be diluted for use intravenously, and injected deeply intramuscularly.

2. A marked adrenergic blockade is sometimes produced. Fairly severe falls in blood pressure were encountered which were often completely refractory to ordinary doses of vasopressors.

3. The awakening period was prolonged. Some patients remained semi-comatose for several hours making care in the recovery room mandatory.

4. The myanesin-like action of Largactil was noted in the recovery room also. The patient appears flaccid with general loss of muscle tone, and the chin must be held to maintain an airway. These patients are usually easily roused, but when left will lapse into sleep and become obstructed.

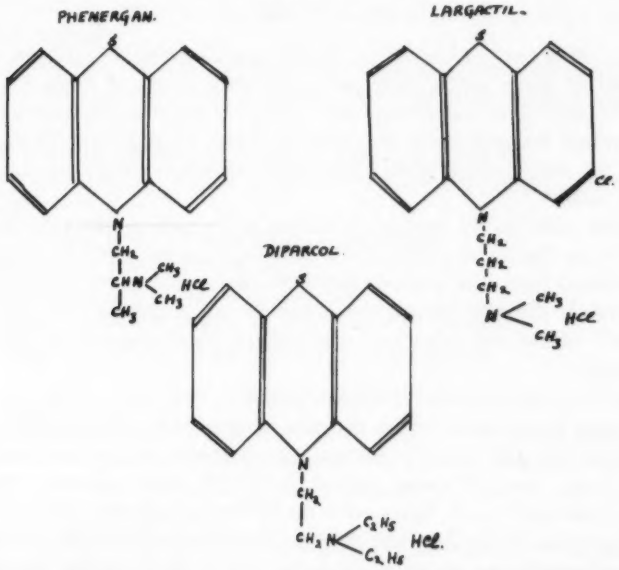
5. Perhaps Largactil's greatest disadvantage is its unpredictability. Small doses have produced fairly severe depression in some cases, while large doses often appear to have little effect. We were completely unable to predict what any given dose would do to any given patient.

6. Finally, it was felt that equally good anaesthesia can be achieved with our usual combined or balanced techniques. The drugs used, i.e., Pentothal, Demerol, Procaine, Curare, etc. are more predictable and patients rouse more quickly post-operatively.

Largactil in Combination

In the search for a better method of using Largactil, it was decided to try a technique suggested by Baxter, Bolster, and McKecknie (2) of Inverness. They use the three Phenothiazine derivatives together, i.e., Largactil, Diparcol, and Phenergan. Phenergan is active antihistaminic and has definite hypnotic properties. Diparcol, a drug used in Parkinson's disease, is noted mainly for its parasympathetic blocking action, and its relief of muscle spasm. Like Phenergan and Largactil, it has a definite hypnotic effect. The chemical formulas of these three drugs show how closely they are related (Figure 1).

FIGURE 1



Their technique is as follows: The usual h.s. sedative is given. One hour preoperatively Phenergan 50 mgm., Demerol 100 mgm., and Atropine 1/100 are injected intramuscularly. The patient arrives in the operating room well sedated and fifteen minutes peroperatively a mixture of Diparcol 250 mgm., Demerol 100 mgm., and Largactil 50 mgm. in 20 cc. of distilled water is injected intravenously over five minutes. The patient goes gradually and pleasantly to sleep and the full effect is observed in about 15 minutes, when further anaesthesia, if needed, is commenced. This "Potentiating solution" as the authors call it, has been used at Shaughnessy Hospital in a short series of cases—fifteen in number.

Total number of cases receiving Potentiating solution—15
Average age of patient—59.7 (30–85) years.
Average weight—143 lb.
Average duration of operation—1 hr, 40 min.

Type of operation:	Gastrectomy	1
	Laparotomy	1
	Colostomy	1
	Lumbar sympathectomy	4
	Left inguinal hernia	1
	Nephrectomy	2
	Smith-Petersen Nail	1
	Caldwell-Luc	1
	Plastic graft to thigh	1
	Burn dressing and skin graft	1
	Arteriogram	1
	Total	15

Seven of the 15 patients required no supplemental anaesthetic agent other than N_2O–O_2, but of these seven, four required small doses of Flaxedil either for intubation or for relaxation during the course of surgery. The remaining eight patients required the addition of Pentothal in doses varying from 75 to 200 mgm., which was the largest dose given. Two cases required small amounts of cyclopropane as well.

All patients were easily intubated, eleven with only a previous 10 per cent cocaine spray to the vocal cords. The remaining four required a relaxant before the endotracheal tube was passed, but Pentothal was not necessary.

Three patients did not require the entire 20 cc. of potentiating solution, one received half, while the other two were given three-quarters of the contents of the syringe.

When the mixture is injected it should be done slowly into a large vein through a small needle. Quick injection or the use of small superficial veins will sometimes produce a marked local reaction characterized by redness and oedema around the veins. One particular patient showed a rather alarming reaction but this process subsided in 48 hours with no further symptoms.

After approximately half of the solution has been given, the patient begins to lose consciousness. An elevation in pulse rate of 10–20 points was noted and the B.P. showed a slight drop which soon returned to normal. The maximum effect comes on approximately 15 minutes after the injection has been completed when the patients were intubated and surgery begun. Many patients showed a rather marked pallor about the face, appearing as if in shock, but in all cases the skin was warm and dry and the pulse and blood pressure stable.

Breathing was quiet and effortless—remarkably so in one asthmatic patient.

On the three occasions in the series when marked blood pressure drops were noted, they occurred after surgery had been established. The drops corresponded with change in position in two cases, and with traction under light anaesthesia in the third.

All other cases in the series were considered smooth, uneventful anaesthetics.

None of the patients were conscious at the end of the operation and did not awake until 3–4 hours after injection of the mixture. Once awake they remained in a rather somnolent state but were easily aroused, co-operative, and rational

when questioned. Nursing care was considered easier and there was no nausea or vomiting. Rectal temperatures were taken every 15 minutes in the post-anaesthetic recovery room and a typical chart shows a temperature of 96° or 97° rising slowly to normal over three hours.

When a group of fifteen control cases were compared with this series, it was noted that when the potentiating solution was used, sedation required during the 12 immediately postoperative hours was markedly reduced. This reduction was not apparent, however, during the following 36-hour period when approximately the same amount of sedation was required in both groups.

The results of this study have been encouraging. It is possible that the combination of Largactil with Phenergan and Diparcol produces a more balanced autonomic blockade, some of the disadvantages of Largactil alone being eliminated in this manner.

In spite of the small number of cases recorded, the results do seem to suggest the following conclusions about Largactil in combination with Phenergan and Diparcol:

1. The amount of anaesthetic agents required is reduced.
2. The patients require less postoperative sedation during the first 12 hours after surgery.

Other favourable clinical impressions have been:

1. The lack of nausea and vomiting.
2. The short recovery period after surgery.
3. The apparent lack of shock in old, poor-risk patients.

We feel that this method deserves further investigation.

Summary

Largactil has been used in Shaughnessy Hospital in a total of 330 cases. The drug was used intravenously during surgery, and orally and intramuscularly in conjunction with usual premedication. In general the intramuscular route was felt to be the most satisfactory.

Although Largactil did appear to have some advantages—such as reducing the amounts of anaesthetic agents required and promoting smooth operative and postoperative courses in the aged—it was felt that its disadvantages outweigh the advantages. These disadvantages may be listed as follows:

1. The drug is irritant to tissue.
2. A profound adrenergic blockade is sometimes produced with associated marked drop in blood pressure.
3. The awakening period was prolonged.
4. The greatest disadvantage of Largactil was judged to be its unpredictability.

A technique suggested by Baxter, Bolster, and McKecknie was described where three phenothiazine derivatives, Largactil, Diparcol, and Phenergan, were combined. Although only fifteen cases were reported, the patients required such small amounts of supplementary anaesthetic agents during the operation, and made such excellent postoperative recovery, that further investigation of this technique was considered important.

In conclusion I would like to give credit to Dr. W. M. Hall, Dr. D. E. MacKay, and Dr. E. Ritch whose help in the preparation of this paper was invaluable.

RÉSUMÉ

Le Largactil a été administré à l'hôpital Shaughnessy dans 330 cas. Une injection intraveineuse de la drogue a été faite pendant l'opération, oralement et par injection intramusculaire en conjonction avec la prémédication habituelle. En général on est d'avis que la voie intramusculaire donne les résultats les plus satisfaisants.

Quoique le Largactil semblait présenter des avantages — comme celui de réduire les quantités d'anesthétiques requis, et d'encourager des progrès égaux pendant et aprés l'opération chez les âgés — l'opinion est que les désavantages l'emportent sur les avantages. Ces désavantages peuvent être énumérés comme suit:

1. La drogue irrite les tissus.
2. Un barrage adrénergique puissant se produit quelquefois avec une baisse marquée de la pression du sang.
3. La période de réveil est prolongée.
4. Le plus grand désavantage du Largactil est que son action ne peut pas être prédite.

Une technique proposée par Baxter, Bolster et McKecknie a été décrite, où trois dérivatifs de la phénothiazine, le Largactil, le Diparcol et le Phenergan ont été combinés. Quoique 15 cas seulement aient été rapportés, les patients exigeaient des quantités supplémentaires si petites d'agents anesthétiques pendant l'opération, et ont effectué des rétablissements si excellents après l'opération, que l'on considère comme important une étude additionnelle de cette technique.

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LARGACTIL IN ANAESTHESIA*

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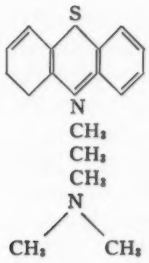
CHEMISTRY

Largactil (Chlorpromazine) is a compound synthesized by the Rhone-Poulenc laboratories of France (RP. 4560) in 1950, and introduced for clinical use by Laborit in 1951 (1). It is one of a series of synthetic compounds derived from phenothiazine. The substance is a white odourless powder, freely soluble in water, chloroform, and alcohol, but insoluble in ether. A 5 per cent solution in water has a pH of 4.0 to 6.5, and is incompatible with thiopentone, gallamine triethiodide (Flaxedil) and decamethonium bromide (Syncurine). (It is compatible with d-tubocurarine chloride and succinyl-choline.) The chemical formula is



PHARMACOLOGY

Although much has been written on the action and the use of Largactil, particularly in the French literature, it is still not clear just where and how the drug acts. The pharmacological knowledge of the drug is still highly theoretical, based on observations of clinical effects. The action appears to be mainly one of depression, particularly of the central autonomic nervous system.

The autonomic nervous system is concerned with those processes which normally are beyond voluntary control and are, for the most part, beneath conciousness. Through its various activities, the autonomic system exercises the important function of maintaining the constancy of the fluid environment of the body's cells. It serves to combat forces, acting either from without or from within, which tend to cause variations in this environment. Regulation of the composition of the body fluids, of their temperature, quantity, and distribution, and perhaps also their metabolism, is effected through the actions of the autonomic nerves upon circulatory, respiratory, excretory, and glandular organs. The stability of

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the internal environment which is characteristic of the healthy body is spoken of by Cannon as homeostasis. According to Cannon (2), the essential and particular function of the autonomic system is to bring about the internal adjustment upon which this constant state depends.

Laborit postulates that the autonomic system overadjusts or overshoots the mark in attempting to restore homeostasis, in the reaction to stress, and that equilibrium is only restored after hours or days. This "counter shock" phase of Laborit stimulates the endocrine defence mechanism (the stress reaction of Reilly and of Selye), i.e. the autonomic-hypothalamus-pituitary-adrenal cortex system, resulting in such things as hyperthermia, negative nitrogen balance, tachycardia, weight loss, sweating. Laborit and Huguenard (3) investigated various phenothiazine derivatives, in an attempt to stabilize the autonomic nervous system, and to lessen the hormonal reaction. From this evolved Largactil.

Largactil is said to be ganglioplegic, vagolytic, sympatholytic, and slightly anti-histaminic.

1. *Central Effects*

Largactil has a blocking action on the activity of the autonomic ganglia of the hypothalamus. It is through this blockade that the autonomic stimuli of stress are thought to be prevented from reaching the pituitary gland. It is also possible that this hypothalamic blockade dampens the appreciation of pain, as the pain tracts pass through this area on the way to the cerebral cortex. The body's awareness of its environment is through proprioceptive reflexes, which also pass through the hypothalamus, and the dampening of these reflexes might account for the state of indifference to the environment that is noted in concious patients given Largactil, rather than a direct cortical depression. There is a reduced response to central nervous system stimulants such as coramine, nikethamide, caffeine, and amphetamine. There is a loss of temperature control, and it is reported that an actual hypothermia occurs, perhaps by depression of the temperature-regulating centre, or because of the peripheral vasodilatation with its increased heat-dissipating effect. Largactil has been reported as an effective anti-emetic against apomorphine (4). Finally there is a potentiation of the action of hypnotics, analgesics, and general anaesthetics.

2. *Peripheral Effects*

Largactil is said to block the autonomic ganglia and also to be vagolytic. This blocking action results in peripheral vasodilatation and postural hypotension, tachycardia, and reduction of the autonomic vasopressor reflexes and loss of sweating. Largactil reduces or reverses the hypertensive effect of adrenalin, comparable to dibenamine, but the effect of noradrenalin is not changed.

Use of Largactil in Anaesthesia

From the above discussion, Largactil could have a definite place in clinical anaesthesia as a sedative, in potentiation of general anaesthetics, as an aid in the technique of induced hypothermia, and to reduce postoperative emesis. Pre-operative sedation with 25–50 mgm. of Largactil without hypnotics or analgesics

produces a tranquil, quiet, co-operative patient, asleep but not depressed. The induction of general anaesthesia is smooth, rapid, with no excitement and little or no coughing on intubation. Similarily Largactil may be useful in the post-operative period for sedative substitution, in reducing pain and discomfort, with little depression, unless combined with the usual dosage of analgesics or narcotics.

It is generally agreed that Largactil does potentiate general anaesthetics, both intravenous and inhalation. This poteniation occures even when Largactil is used as a preoperative sedative, and particularily so when given during anaesthesia. This effect is of some importance in the elderly and poor-risk patients, who can be maintained in a light plane of anaesthesia, with less of the depressant agents. In some instances, repeated preoperative and operative use of Largactil has produced a state of anaesthesia, where surgery can be carried out without other agents.

Finally Largactil may be a useful adjunct in the technique of induced hypothermia for intracardiac and intracranial surgery. It in itself may lower the temperature somewhat, and reduce the cooling time and the amount of analgesia or anaesthesia necessary to prevent shivering.

Clinical Study

Since Hudon of Quebec introduced Largactil into this country (5), much discussion and interest have been aroused over it. Our curiosity was aroused as to whether Largactil does in fact decrease the stress reaction to surgical trauma, potentiate anaesthetics, reduce blood loss during surgery, and reduce the amount of postoperative narcotics. We were curious to determine whether there was really any advantage in its use, or whether the promoters were a little over-exuberant.

We have used Largactil in a small series of 144 cases of major surgery, mainly gastro-intestinal resections, pelvic and thoracic and neck dissections. The age of these patients varied from 17 years to 80 years. The average age was 37.5 years. The drug was used in the following five ways:

1. Premedication: 25–50 mgm. intramuscularly or intravenously (slow drip), with and without other sedatives.
2. 25–50 mgm., single dose or repeated after 3 hours, during anaesthesia, associated with all commonly used anaesthetic agents.
3. Administered during anaesthesia and for a variable time every 4–6 hours in the postoperative period up to 48 hours.
4. Administered in the postoperative period alone.
5. As above, with and without Phenergan, 108 cases with Largactil alone, 36 cases with equal dosage of Largactil and Phenergan.

Observations

Our observations on the effects of Largactil have been varied, but on the whole agree with those of other observers. It must be admitted that it is easy to become over-enthusiastic, and that clinical observations are very apt to be exaggerated in favour of the drug.

1. *Sedative Effect*

Largactil, with or without Phenergan, does produce a tranquil state, or a state of indifference. Some patients, particularly women, who are known to be nervous and excitable, come to the operating room quiet, usually with their eyes closed, but will respond to questioning and are co-operative. They take no notice of the surroundings and don't object to vena-puncture. They are depressed but not in the same sense as with morphine—there is no comparable respiratory depression particularly in the elderly.

2. *Potentiation of Sedatives, Anaesthetics, and Relaxants*

The preoperative and postoperative effects of analgesics for sedation are definitely enhanced, and their side reactions of respiratory and cerebral depression increased, in some cases alarmingly. If morphine or Demerol have to be given, ½ to ⅓ of the dose would suffice. Codein and aspirin would probably be sufficient in most cases.

All inhalation and intravenous anaesthetic agents were potentiated by Largactil. It was difficult at first to judge the proper amount of cyclopropane and diethyl ether which would maintain light anaesthesia without producing profound and prolonged postoperative depression. When Largactil was given as a sedative, the sleep dose of thiopentone required was much less than expected. After the drug was used in combination with all agents, the best combination was thought to be undoubtedly nitrous oxide and intravenous Demerol or nitrous oxide with Trilene. From the standpoint of postoperative depression, it was amazing in many cases to find how little general anaesthesia was required.

There appeared to be a potentiation of all relaxants. This was true of d-tubocurarine, gallamine triethiodide, decamethonium bromide, laudolissin, and succinylcholine. Good abdominal relaxation could be obtained and maintained for longer periods than expected with a dose of relaxant considered to be smaller than usual.

The various anaesthetic agents and combinations with which Largactil has been used in this series are shown in Table I.

TABLE I

ANAESTHETIC COMBINATIONS WITH LARGACTIL

Demerol/N_2O/O_2	34
Pentothal/N_2O	21
Cyclopropane	48
Ether	22
N_2O/Trilene	19
Total cases	144

3. *Cardiovascular Effects*

Two effects commonly noted were tachycardia and hypotension. These occurred no matter how slowly or quickly or by what route the Largactil was given, or with what other agents it was used. However the occurrence of hypotension was more common and more profound when Largactil was given (quickly)

intravenously, and when the patient was so positioned as to favour pooling in the lower extremities. At the personal suggestion of Laborit, we then combined Phenergan with Largactil in equal amounts and found hypotension to occur less frequently.

Hypotension occurred in all but fourteen of the cases, and the drops in systolic pressure varied from 10 to over 70 mm. Hg. In cases where the fall was greater than 30 mm. during operation, it was usually associated with an operative position conducive to pooling of the blood.

In two cases where 50 mgm. of Largactil were given in slow intravenous drip as a preoperative sedative, combined with ⅙ gr. morphine and 50 mgm. Demerol respectively, the blood pressure fell from 205/90 to 130/80, and 165/80 to 128/65 in one hour prior to induction of anaesthesia. This profound fall in pressure was not noted when these analgesics were omitted. In those cases where the fall in pressure was over 30 mm. Hg., and where the patient was in a pooling type of position, the hypotension remained throughout the duration of the operation and on into the postoperative period. This prolonged hypotension was not viewed with alarm except in the elderly and poor-risk patient. Hypotension associated with Largactil is difficult to reverse, in contrast to that caused by the hexamethonium salts and Arfonad. Pressor drugs, such as Methedrine, had little or no effect or only a mild temporary effect. To raise the pressure one had to resort to the use of blood transfusion, plasma expanders, or noradrenalin. In most cases, however, the hypotension was allowed to continue, and the pressure gradually returned to normal in from 15 minutes to 5 hours. However this prolonged hypotension into the postoperative period, especially if associated with anoxia, confused the picture and it could possibly mask postoperative haemorrhage.

In most cases, it was estimated that blood loss was reduced, and in many cases the loss was nil. No accurate measurement of blood loss was made, but the reduction in blood loss was thought to be largely due to the hypotension. In five cases hypotension was deliberately induced with hexamethonium or Procaine amide, little of either being necessary.

The hypotension experienced in this series is tabulated in Table II.

TABLE II

Mm. Hg. fall	Normotensive—up to 140 mm. Hg.		Mm. Hg. fall	Hypertensive—over 140 mm. Hg.	
	Operative	Postoperative		Operative	Postoperative
0	37	14	0	1	0
0–10	15	8	0–10	0	0
10–20	12	8	10–20	2	1
20–30	14	15	20–30	2	0
30–40	19	24	30–40	3	0
40–50	12	23	40–50	3	0
50×	16	18	50×	6	10
	125			17	1
Total	142				

4. *Postoperative Period*

Postoperative depression and delay in regaining consciousness was a common observation. As noted previously this was particularly so when either cyclopropane or ether had been the principal anaesthetic agent, even in minimal amounts. The least depression, and the smoothest postoperative course was when Largactil (with or without Phenergan) had been combined with a small dose of Thiopentone (usually less than 250 mgm.), Demerol (usually under 100 mgm.) and nitrous oxide.

On regaining conciousness, the patients appeared more comfortable and in less pain and more co-operative than those who had not received Largactil. This was particularily noticeable in the recovery room with two patients who had had the same operation, one with Largactil, the other without. At the end of the first 24 hours, patients who had received Largactil (even only one dose) appeared more comfortable, their skin was warm, dry, and pink, they were more cheerful and relaxed and in many cases hungry.

The need for postoperative sedation was thought to be reduced, although this observation has not been controlled. The average time for the need of the first sedative was 6–8 hours, varying from 1 to 24 hours and ten cases (all major surgery) required none. This was difficult to assess, for in many cases we felt that sedatives were given unnecessarily. Sedatives if necessary had to be given cautiously with reduced dosage, even 10–12 hours after the Largactil had been given, otherwise depression of cough and respiration would occur.

Postoperative emesis was conspicuous by its near absence, occurring in 8.3 per cent of cases, a percentage which is significantly lower than that found in unselected non-Largactil patients reported elsewhere (41 per cent) (6).

Postoperative urinary retention occurred frequently, over 12 hours in 54 per cent of the cases, and 20 per cent of the total had to be catheterized in the first 24 hours.

5. *Laboratory Studies*

In an attempt to investigate the effect of Largactil on the stress reaction, some laboratory studies were made. It is generally agreed that a fall in the total eosinophile count below 50 per cu. mm. is a measure of an adequate adrenal response to stress. This response can also be demonstrated by measuring the 24-hour urine steroid output.

According to Laborit (3), Largactil diminishes the autonomic stimulation of the pituitary gland, and thus either blocks or decreases the pituitary-adrenal response; in other words it blocks the stress reaction. If this be so, the postoperative eosinophile counts and urine steroid levels should remain relatively normal, indicating little or no adrenal stimulation.

Our observations, although made only with a few cases, and certainly not conclusive, do not bear out this hypothesis. In the cases studied, Largactil did not significantly alter the stress reaction as far as it was measured by preoperative and postoperative eosinophile counts and urine steroid levels.

The results of these investigations are shown in Table III.

TABLE III

Case	Largactil	Total Eosinophile per cu. mm.		Urine 17 Ketosteroids per 24 hr.		Urine Corticoids per 24 hr.	
		preop. day	postop. day	preop.	postop.	preop.	postop.
Lobectomy	None–control	311	22	4.8	8.7	1.7	3.5
Decortication	50 mgm.	288	22	1.4	3.6	1.3	5.0
Lobectomy	175	100	0	—	—	—	—
Lobectomy	100	231	5	2.5	2.9	2.2	6.4
Thoracotomy inoperable	100	144	77	—	—	—	—
Total gastrectomy spleenectomy	100	88	55	—	—	—	—
Vaginal hysterectomy	50	154	22	1.6	4.2	0.8	1.9
Excis vulva & bilateral inguinal block dissection	50	55	0	3.3	4.4	1.0	3.6

6. *Discussion*

From our experience with Largactil in anaesthesia we feel that the drug has a definite place in our armentarium and particularly for poor-risk patients and in major surgical procedures. We feel that in this respect its value lies principally in the reduction of the quantities of more depressing and toxic agents required for satisfactory surgical anaesthesia, and in the reduction of the postoperative reaction of the patient to pain and trauma. We feel that this drug should not be used simply as an adjunct to usual anaesthetic techniques, but rather consider its use to require new and almost homeopathic concepts in the administration of other agents.

Our studies have not borne out the theory that this drug abolishes the normal pituitary-adrenal reactions in response to stress, although our observations of the general effects of the drug on the surgical patient correspond with those reported by others.

We think it worthy of note that in spite of the frequent occurrence of prolonged postoperative depression in our series there has been no notable increase in the postoperative complications which one might expect this to produce. There have been two cases of postoperative pulmonary atalectasis, one coronary thrombosis, and one unexplained late hypotension occurring 12 hours post-operatively. Four patients died in hospital of surgical complications unrelated to anaesthesia.

Postoperative vomiting is reported in 8.3 per cent of these cases, but no patient had serious vomiting, and with one exception these patients vomited only once, and usually 4–8 hours postoperatively.

7. *Other Uses*

We are studying the use of Largactil in the control of hyperemesis gravidarum, in the anaesthetic management of the normal obstetrical patient, in the control of intractable pain, and in the management of generalized hypothermia for cardiac and neurological surgery. These matters will be the subjects of further reports.

Summary

This report has dealt with observations made on the use of Largactil in 144 patients undergoing major surgical operations. Its action as a preoperative sedative drug and in the potentiation of action of anaesthetic agents and relaxants during operation has been described. The effect on the postoperative period has been discussed, and data relevant to the complications encountered in its use have been given. Some laboratory investigations relating to its effect on the physiological responses to stress are tabulated.

Résumé

Les auteurs ont rapporté des observations faites au sujet du Largactil en anesthésie dans 104 cas de patients subissant des procédés chirurgicaux majeurs. On a découvert que la drogue augmentait l'action des anesthétiques et des sédatifs. Lorsqu'elle est administrée seule, elle a causé de la tachycardie et de l'hypotension chez la plupart des patients. Ces effets ont été réduits lorsque la drogue a été employée en association avec le Phenergan en quantités égales. Dans le plus grand nombre de cas, on a estimé que la perte de sang était réduite, cette réduction de saignée étant attribuable à l'hypotension.

Durant la période post-opératoire un réveil retardé devient une observation commune, en particulier lorsque le cyclopropane ou l'éther constitue l'agent anesthésique principal. Une dépression moindre et une evolution post-opératoire plus égal ont été observés lorsque le Largactil (avec ou sans Phenergan) a été combiné à une petite dose de Thiopentone, de Démerol ou de Protoxyde d'Azote. La nécessité du sédatif après l'opération a été réduite et les sédatifs lorsqu'on a dû y avoir recours ont été nécessairement administrés soigneusement et en doses considérablement réduites afin d'éviter la dépression respiratoire et la toux réflexe. Les vomissements après l'opération ont été rares. La rétention d'urine après l'opération a été fréquemment observée.

La mesure avant et après l'opération d'excrétion urinaire stéroïde et la réponse éosinophile dans un petit nombre de patients n'ont pas démontré une altération appréciable des réponses pituitaires-adrénaline au « stress ».

Acknowledgment

We wish to acknowledge the kindness of Poulenc, Ltd. in supplying the drugs used in this study.

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ON CERTAIN MEDICAMENTOUS SYNERGIAS IN INDUCED "BIOCEMESIS" (ARTIFICIAL HIBERNATION)

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THE expression "medicamentous synergia" means the use of products whose pharmacodynamic properties act together, enhancing or completing one another —"potentializing one another" as Huguenard writes (9).

The term "biocemesis" is a new one, characterizing a state of slower life, close to hibernation. It comes from the Greek and is literally the action of wearing away. We borrowed it from Colonel Jaulmes, because it best expresses the type of anaesthesia which we are going to present; that is to say, a decrease of the neurovegetative life, obtained solely with drugs and the utilization of cold. We are edging away more and more from the purely sensory anaesthesia, which often produces shock and shows adrenalin-like effects, such as anaesthesia with ether. We are therefore aiming towards anaesthesia with few or no anaesthetics, towards anaesthesia of the reflex arc, and towards a neuro-humoral and a neuro-endocrine anaesthesia (pituitary, adrenal, and thyroid).

The idea is not new. It was not conceived strictly from intuition, but is the result of the study of the problem of "shock," which for years has disturbed research workers. Claude Bernard brought forward the notion of the "internal milieu"; Cannon spoke of "homeostasis," and Leriche of "postoperative disease." Reilly and Selye, in demonstrating the nature of organic responses to aggression, featured the neurovegetative system and the neuro-humoral (endocrine) system.

It is mainly to Professor H. Laborit of the Military Hospital of Val-de-Grâce, Paris, that we owe a good symposium resulting from all the previous ideas and from subsequent research work. Laborit has published extensively on this subject (10, 11, 12, 13, 14, 15), and he and his associates have summarized the state of this question in all fields of medicine. In 1953, Professors Hudon and Jacques also presented a study of the problem of hibernation (8). All these studies would seem to revolutionize certain concepts not only of anaesthesia, but also of various aspects of medicine and therapeutics as a whole.

Let us take as examples to illustrate this evolution the premature baby, and the baby born in a state of duress. It has always been classical to treat premature infants by combating cooling with the aid of incubators. We act in exactly the same way when we deal with babies born in a state of duress due to cerebral anoxia following a hard delivery, prolonged compression of the cord, or manoeuvres of forced traction. In both cases, these babies are placed in an incubator and covered with very warm clothes, which scarcely give them the necessary freedom to breathe. The resulting picture is always the same: hyperthermia, profuse sweating, polypnea, tachypnea, atelectasis, convulsions, cyanosis, and very often death.

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Now let us describe the clinical picture of two of our recent cases. They are baby P— and baby M— born at an interval of one hour, both after a very difficult delivery. Both of them were revived only after intubation, oxygen therapy, and respiratory stimulants given intravenously, all this taking one hour before the first spontaneous respiration. Both eventually showed the syndrome previously described, i.e. hyperthermia consecutive to cerebral anoxemia.

Baby M— is placed in an incubator, has on too many clothes, and is given too much heat. He sweats profusely, his temperature rises to 106°F., in the 36 hours following his birth. He dies within 48 hours, literally "consumed."

Baby P— is placed in the same room. He is just laid in bed and is given oxygen. Within 8 hours, his temperature has already risen to 105°F. and he also manifests stiffness in the neck and convulsive episodes. To the horror of the medical personnel, the baby is cooled down to 96°F. in a tent with ice, under a concentration of 40 per cent oxygen. The baby is naked. He receives 2.5 mg. of Phenergan intramuscularly every 5 hours, 5 cg. of Gardenal every 6 or 8 hours and subcutaneous serum. After seven days of this treatment baby P— is removed from the tent. He is alive and can have some nourishment.

We do not wish to make a general conclusion after only two cases, but we do wish to state that babies born with the syndrome of hyperthermia as well as premature infants would perhaps benefit more not by heating, but by cooling after neuroplegia. As David states, it would be preferable to hibernate them in order to help them pass through this critical period of their commencement of life.

The problem is the same for the premature infant. He is a tiny being not capable of raising or maintaining his metabolism to the indispensable level which would assure his thermogenesis, his tissue life, and his growth. Very often, the application of very warm conditions to reduce the difference between his capabilities and his needs is a complete failure. Let us, then, consider the question of cold for premature babies.

We should consider the premature baby as suffering from "shock" and as a patient in whom, according to Laborit, "in decreasing the tissue needs, one could expect to create a new equilibrium through which the organism could acquire its normal functional state, not recuperate as does the adult."

Again, we do not pretend to solve the problem by mentioning two casual cases, but we wish to present the viewpoint that hibernation is applicable to the premature infant as well as to the baby born with cerabral anoxia.

The human being has developed and improved himself, and, by so doing, has acquired freedom in relation to external states. He does not adapt himself any more to environment but tends to adapt these external conditions to his own requirements. He has improved his defence mechanism by conditioning his autonomic nervous system, visceral and hormonal, which evolves independently of his individual will.

The higher being evolves according to an imaginary equilibrium called "Health," with constant oscillations which are not noticeable as long as they do not exceed the defence limit of the organism. However, any attack on this mean is considered as an aggression against which the organism reacts in a very specific

and very well-defined way. Disease is an aggression. Trauma is an aggression. Surgical intervention is an aggression which may lead to operative disease and death, by exhaustion of the reactive capabilities of the organism.

The well-evolved being reacts to aggression by increasing his combustion and his exchange in opposing to the maximum this environment in which he is and which is aggressive to him. Therefore, there is a certain wavering around his lost equilibrium, a biocatalytic wavering in which calcium, potassium and all electrolytes take a part. Histamine, acetylcholine, adrenalin, gluco- and mineralocorticoids, and all endocrine secretions also play their part.

To summarize, any surgical operation constitutes an aggression against the organism. Following this aggression there is a phase of immediate disequilibrium —a phase of more or less severe shock commensurate with the severity of the aggression. The organism, through its autonomic nervous system and its chemical agents (of which adrenalin comes first), reacts to this state of immediate shock by a catabolic phase, i.e. through adrenalin, then through the pituitary gland with gluco-protidic incidence on the adreno-cortex. This phase lasts four to five days on the average. It is a sympathicomimetic phase, destructive to the proteins. It may cause thrombosis and prevents cicatrisation. Then comes the anabolic phase of compensation which is vagal, acetylcholinic, and characterized by its mineralocorticoids. This passage from the adrenalinic state to the vagal one is very often marked by grave accidents: it is the vagal crisis of the fourth or fifth day following operation, with hypotension, lipothymia, cold sweating, infarctoid accidents, and at times collapse and embolic accidents. Towards the end of this period, that is from the sixth to the tenth day, the balance is re-established. The protein rate comes back to normal, appetite is felt again by the patient, and the weight increases. All the digestive functions resume their activities.

Such is the picture following operation as we see it at present. We have borrowed it from the synthesis of Laborit, and after ten years of clinical research work aiming at a neuro-vegetative equilibrium in anaesthesia, we have come to the same conclusions as Laborit and his associates.

Endocrinologists and biologists also agree on such an explanation of shock and we feel it will prove advantageous to carry on experimental work on the same line.

Laborit uses a pituitary somatotrope extract called Somatrophine (S.T.H.) in general surgery, in order to counteract the action of the adreno-corticotrope pituitary hormone. With this hormone, he wishes to accomplish on the endocrinological plan what is realized with Largactil on the pharmacodynamic one. The idea is the following. The patient who is hibernated, in a state of "slower life," with a lowered metabolism, does not use his hydrocarbons, but does utilize his proteins and his lipids. Somatrophine is employed to reduce the use of protides, to prevent the utilization of glucose, and to mobilize the catabolism of lipids. Thus, it is not only the neuro-humoral activity which is depressed but also the neuro-endocrine activity.

We have not yet had the opportunity of using this hormone but we take the precaution of injecting proteins intravenously in cases of hydration occurring during or after operation, in order to combat this protein deficit of the plasma and thus to avoid lumbar bed-sores in patients immobilized for a long time.

Let us now describe what we are doing and what research workers have brought about in the field of anaesthesia. We shall see whether or not the condition of the patients has been improved and if so, in what way.

In routine surgery, cases of total hibernation, either pharmacodynamic or hypothermic, are rather unusual. However, what we may call semi-hibernation is often practised, meaning that a neuro-vegetative balance is established on the day preceding the operation and is terminated in the first few hours following it.

Every aggressive action calls for a counter-reaction which is as strong or disastrous as the aggression has been violent. If we succeed in decreasing or, if possible, in suppressing this aggressive action at its very onset, we thus decrease the counter-reaction. This idea may apply to any case of surgery.

The problem varies with the facilities of each anaesthetist. In our hospital, we had to eliminate what seemed to be the complicated points of the technique and aimed at the most practical method for our patients, that is to say, at the suppression of the aggression at its starting point and hence, at the prevention of shock. We attempt:

1. The suppression of the emotional aggression by a visit to the patient before the operation and then the elimination of anxiety through persuasion and premedication during the day or days preceding the operation.

2. The suppression of the aggression during the operation by blocking all the possible irritations from the afferent pathways of the reflex arc, the centres, and the efferent pathways. This blockade is carried on during the day or days following the intervention.

With this object in mind, we utilize the following pharmacological products in appropriate fashion:

(*a*) Barbiturates such as Carbrital, Pentothal and Surital.
(*b*) Antihistaminics such as Phenergan and Benadryl.
(*c*) Neuroplegics such as Largactil or Neocaine and Methonium salts.
(*d*) Analgesics such as Demerol.
(*e*) Curarizing agents such as Syncurine and Flaxedil.

Postoperatively we use Sparteine in patients free from troubles of auriculoventricular conduction, Magnesium Sulfate, Prostigmine, and Demerol. We do not use Atropine which is "antibiocemetic." Induction barbiturates, such as Pentothal or Surital, are used only as starters and as a rule the dose never exceeds 350 mg., whatever the duration of the operation.

One of the products to which we wish to draw attention is the derivative of Phenothiazine, R.P. 3277 (Promethazine or Phenergan or Fargan or dimethylamino-2′-methyl-2′-ethyl-N-dibenzo parathiazine hydrochloride.) This product possesses pharmacodynamic properties and promotes actions which are most valuable:

1. Blockade of the afferent pathway of the reflex arc (therefore, suppression at its starting point of surgical irritation caused either by manipulation or traction, and thus a decrease in the counter-reaction).
2. Hypnotic and amnesic action.
3. Antalgic action.
4. Hypometabolic action.
5. Antibiotic action.

6. Anti-shock action by the diminution of capillary permeability, by the re-establishment of the pre-capillary sphincter action, and by the diminution of the chemo-sensitivity of the carotid glomus.

7. Diuretic action through diminution of the sensisivity of renal tubules.

8. Inhibitor hypophysial action.

9. Anti-emetic and antihistaminic action.

We use Phenergan intramuscularly as premedication; during the operation we use it intravenously, diluted in a solution containing either Largactil (R.P. 4560), Neocaine or a Methonium salt, and Demerol. We also use it post-operatively by the intramuscular route and more rarely by the intravenous route. The average daily doses range between 200 and 250 mg.

The pharmacological properties of Demerol, Procaine, Largactil (R.P. 4560) and other Phenothiazine derivatives are all well known. The Phenothiazine derivatives have become the symbol of pharmacodynamic hibernation. We will not enlarge upon their pharmacodynamy.

Let us now analyse the picture of a patient undergoing rather a serious surgical operation.

During the night preceding the operation, he sleeps following 100 mg. of Benadryl and 1½ to 3 grains of Carbrital, which exerts a sedative action on the cortex.

On the morning of the intervention, the patient will receive, by the intramuscular route, 50 mg. of Phenergan and 100 mg. of Demerol; or he will be given a barbiturate, 1½ hr. before the operation, and, just 1 hr. before, an intravenous infusion of a solution containing 50 mg. of Largactil, 50 mg. of Phenergan, and 100 mg. of Demerol.

When he is taken to the operating room, he is in a state of complete lobotomisation. During the operation, the operative shock is combatted with these products whilst a close supervision is kept of the electrolyte, protein, and blood balance. The barbiturate doses for the induction of the anaesthesia are small. An adequate and constant curarization is maintained during the whole intervention. All the patients are intubated. The control of respiration is a routine. During the operation, the heart is controlled by the electronic cardioscope and the central and peripheral temperatures are controlled by a thermocouple.

Leaving the operating room, the patient is in a unique state of twilight sleep, which will not prevent him from answering questions, but which will keep him amnesic to all the following infusions. In normal postoperative cases, we keep on injecting 50 mg. of Demerol together with 1 cc. of prostigmine (1:1200), as required.

Sparteine and Magnesium Sulfate are injected if necessary. We have been using these products for a year and a half.

We have noticed the following *inconveniences*:

1. Dryness of mouth, lips and tongue.

2. Elimination or diminution of hydrochloric acid in the stomach, and therefore stomach pains at the awakening.

3. The patient cannot get up from bed as early after operation, and at times manifests agitation, due to this medicamentous lobotomy.

4. Closer supervision is necessary.
5. Drainage of the bladder with a catheter is almost obligatory.

In spite of these inconveniences, we, and our medical personnel, could see the following *advantages*:

1. Use of narcotics is decreased 90 per cent.
2. Meteorism, distension, dilatation of stomach, intestinal flatulence, and vomiting are almost completely eliminated.
3. The electrolyte balance is more easily maintained.
4. Pulmonary complications are prevented.
5. Postoperative embolus or postpartum phlebitis are absent. There are marked advantages. The necessity for getting up from bed early is eliminated. Considering that adrenalin (as digitaline) blocks the secretion of heparin at the mast cells, if we eliminate the adrenergic phase we thus favour the increase of heparinemia and therefore the decrease of prothrombin time. In our opinion, this is a most valuable advantage.
6. Finally, the temperature during operation, controlled by the thermocouple, is lowered by three or four degrees F., compared to a rise of one to three degrees F. during usual anaesthetic procedure.

Let us summarize a few clinical observations:

(*a*) Mrs. A.P.B., 65 years of age, undergoes a laparotomy for total hysterectomy, double salpingo-ovariectomy, appendicectomy, and cholecystectomy for a calculous subacute cholecystitis. All this surgery was performed during one intervention. The patient received the usual premedication, i.e. Carbrital, Phenergan, Demerol. The administration of solution No. 1 containing 50 mg. of Largactil, 50 mg. of Phenergan, and 100 mg. of Demerol, diluted in 500 cc. of 5 per cent glucose serum, was started three-quarters of an hour before the operation and maintained until the suture of the peritoneum. Blood loss was evaluated at 300 cc. During the operation, the patient received only 200 mg. of Pentothal for induction and 8 mg. of Syncurine, plus oxygen and nitrous oxide inhaled through the endotracheal tube. Following the operation, the patient was given only 50 mg. of Phenergan intramuscularly every sixth or eighth hour, for 72 hr. No narcotic was administered; the patient did not suffer from any nausea, vomiting, or distension and the third day, when Phenergan was stopped, the bowels functioned normally. She got up from bed and did not complain of any pain.

(*b*) M.O.D., 68 years old, underwent a cholecystectomy for acute calculous cholecystitis. This is a case similar to the previous one. After the operation, the patient had only 50 mg. of Phenergan injected intramuscularly every 6 hr. He does not remember anything from the eve of the operation to the third day when he was allowed to get up. The central temperature never rose more than one degree. Although obese and weighing more than two hundred pounds, and a plethoric, the patient had a most normal recovery.

(*c*) Miss Y.D., 20 years old, has to undergo a ligature of the arterial canal. Unlike the first two patients, this one receives solution No. 2 containing Phenergan, Demerol, and Neocaine. During the intervention, there is no alteration of the hemodynamics or of the electrocardiogram. Only 225 mg. of Pentothal

are given and a curarizing agent in the total amount of 9 mg. Following the operation, she is given 50 mg. of Phenergan with 25 mg. of Largactil intramuscularly every 8 hr. No narcotic is administered.

(*d*) Mrs. Y.M., 86 years old, underwent an arthroplasty of the left ankle. Solution No. 4 was injected before and during the intervention. As a sedative, she received only 50 mg. of Phenergan every 8 hr. Recovery was normal.

(*e*) M.G.D. after severe trauma is taken to the hospital in a state of complete shock. It is completely impossible to detect the pulse or the arterial pressure. His face is livid and waxy. Treatment for shock is begun immediately. Two hours later the surgeon is willing to perform an operation. The arterial tension is still not perceivable and the pulse rate is 140 per minute. Solution No. 4 is injected before anaesthesia. One hundred milligrams of Pentothal associated with 4 mg. of Syncurine allow an easy intubation. The control of respiration is started. The surgeon is very surprised to notice that even before any injection other than solution No. 4, the arterial tension has risen to 100 mm. Hg. The patient undergoes splenectomy for rupture of the spleen, left nephroplasty because of laceration, and drainage of a serious retroperitoneal hematoma. Recovery was satisfactory.

(*f*) Baby L—, one month old, undergoes a laparotomy for grafting of the common bile duct. The diagnosis is atresia of the biliary ducts. As a premedication, the baby receives 2½ mg. of Phenergan and 2½ mg. of Largactil by the intramuscular route. During the intervention only a curarizing agent is administered and a mixture of oxygen, nitrous oxide given through an endotracheal tube which allows controlled respiration. The patient is cooled to 32° C. During the intervention which lasts about three hours, his condition remains excellent. The cooling is maintained for three days. No post-operative sedative is given.

We have mentioned this last case to point out the importance of combining neuro-vegetative anaesthesia and hypothermia at times. This baby would have not survived such a serious operation with the old methods of strictly sensory anaesthesia.

Technically speaking we do not follow standard rules, but adapt the above-mentioned drugs to the needs of the individual, according to his physical condition and to the severity of the surgical operation.

Personally, we have agreed to use five different intravenous mixtures for "biocemesis," which we designate as follows:

S^1 stands for a solution containing 100 mg. of Demerol, 50 mg. of Largactil, 50 mg. of Phenergan, diluted in a 5 per cent glucose solution.

S^2 stands for a solution containing 50 mg. of Phenergan, 100 mg. of Demerol, and 1 gm. of Neocaine.

S^3 contains 50 mg. of Phenergan, 40 mg. of a Methonium salt, and 100 mg. of Demerol.

S^4 contains 50 mg. of Phenergan and 1 gm. of Neocaine.

S^5 contains only 50 mg. of Phenergan.

We use one or the other of these solutions according to the surgical intervention to be performed.

We have used Phenergan (R.P. 3277 or Promethazine) during 2,175 operations,

including gastrectomies, pancreato-duodenectomies, hysterectomies, ligatures of the arterial canal, Caesarean sections, and vaginal deliveries. Phenergan was the most used of all the hibernating drugs, either for premedication, during the operation, or after the operation.

Solution No. 1 was used for 165 cases, with 254 for solution No. 2, 28 for No. 3, 112 for No. 4, and 160 for No. 5.

Let us summarize these observations in the following comments:

In our opinion, any anaesthetist who wishes to use this technique must study it very carefully beforehand and know exactly the pharmacology of each one of the drugs involved.

If we seem to have particularly stressed the cautious and logical utilization of Phenergan (R.P. 3277) and Largactil (R.P. 4560) in each case, it is because our experimental work has shown that these products allow us to decrease the amount of barbiturates, narcotics, or anaesthetics used previously.

Phenergan is not as delicate to manipulate as its cousin Largactil, and may easily be applied to every medical field.

As to Largactil, we must recognize its action on the central nervous system, its sedative, hypnotic, hypothermic properties as well as its action on the autonomic nervous system and its ganglioplegic properties. One must not forget the potentiating action of Largactil on Procaine.

It is not necessary to use all the hibernating drugs at the same time, but rather according to the severity of the surgical intervention and to the physical condition of the patient.

The utilization of drugs capable of blocking the transmission and the action of the neuro-vegetative impulse has greatly improved the general state of our anaesthetized patients.

Through potentialized anaesthesia, we were able to improve anaesthesia during and following the operation.

A greater organic protection was obtained against surgical aggression.

The use of narcotics and barbiturates was reduced considerably and, in many patients, totally abandoned.

In conclusion, may we add that the nicest and truest testimonial of this progress in anaesthesia is the observation of many patients that "to be operated upon now is not as hard, painful and complicated as it used to be."

In fact, it is now possible for us to promise the patient that he will be able to go through a surgical intervention without anxiety, without vomiting, without shock, and that he will come out of it without any incident.

RÉSUMÉ

Le terme "Biocemese" est un néologisme du médecin-colonel Jaulmes, de Paris, et indique un état de vie ralentie par l'usage de médicaments seulement sans l'apport du froid.

L'auteur préconise l'anesthésie neuro-végétative pour remplacer l'ancienne anesthésie strictement sensitive, dans le but de prévenir le choc opératoire, l'agression chirurgicale, et d'améliorer les suites post-opératoires. C'est le résultat

des travaux de Reilly et de Selye, et des expérimentations de Laborit et de Huguenard.

L'auteur décrit les techniques utilisées au cours de son expérimentation, et les propriétées des produits utilisés et insiste sur le R.P. 3277 ou Phenergan et sur le R.P. 4560 ou Largactil. Il décrit les avantages et inconvénients de la technique, les précautions à prendre et illustre ses données par la présentation de cas cliniques typiques. Ses résultats, sur 719 cas au moment de la publication, sont des plus prometteurs.

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MIXED PENTOTHAL–CURARE–NITROUS OXIDE ANAESTHESIA FOR CHILDREN AND INFANTS: A TECHNIQUE AND DOSAGE SCALE FOR RAPID INTUBATION AND FOR MAINTENANCE*

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ONE of the most advantageous of the general anaesthetic combinations to arise from the introduction of curare by Griffith (14) was pentothal–curare–nitrous oxide. Moderate doses of these agents produce the main pharmacological effect of each (hypnosis, relaxation, and analgesia) and are relatively free from the morbid side effects of comparable doses of the other general anaesthetic agents. However, these three agents together interfere with pulmonary respiration to a far greater extent than do anaesthetically equivalent amounts of the other anaesthetics, i.e. respiratory centre depression by pentothal, plus respiratory muscle paralysis by curare, plus reduction of compensatory oxygen gradients by effective concentrations of nitrous oxide. This seemingly great disadvantage is at once eliminated by adequate and continuous assisted or controlled ventilation throughout with over 20 per cent oxygen from a non-rebreathing system receiving a total flow of 8 litres per minute of gases (nitrous oxide and oxygen). With adequate amounts of curare excellent relaxation for orotracheal intubation and/or abdominal surgery is obtained under light (plane 1) anaesthesia. Thus the cells of the brain are subjected to only the minimum necessary amount of interference with functional energy build-up (ATP formation (23)) so that associated cellular oxidative processes and hence the vitality of not only the brain but also myocardium, liver, kidneys, endocrine glands, etc. remain relatively unimpaired. The low total dosage of pentothal also keeps its hypotensive effect to a negligible minimum. The resemblance of pentothal–curare–nitrous oxide anaesthesia to natural sleep and artificial hibernation has been noted (15, 16).

The technique of using pentothal mixed beforehand with curare in their optimum proportions (usually as "Baird's solution" (1) of 500 mgm. pentothal with 15 mgm. d-tubocurarine chloride in a 20 ml. syringe or a 500 ml. drip) while it does not give absolute control of either one, gives in return the advantage of technical simplicity with greater smoothness and exactness of over-all control. The overlapping effect of the main pharmacological properties of the three agents coupled with direct control over the concentration of nitrous oxide gives a considerable degree of elasticity to fixed proportions of pentothal with curare, so that absolute dosage control over either of the two drugs is not necessary. In the small percentage of cases where the nature of the patient or operation goes beyond the bounds of this elasticity fairly exact control is easily regained with an accordingly different initial proportion of pentothal and curare or by injecting

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an additional amount of pentothal or curare into the tubing of the original mixture when the need becomes apparent. With opportune tapering off of the dosage before the end of operations, most patients have regained an adequate ventilation of their own and can therefore be extubated and are emerging a few minutes after the operation.

Despite the great preponderance of its advantages over its disadvantages in orotracheal intubation and abdominal surgery in adults, pentothal and curare have found only sporadic use in paediatric anaesthesia. The reason for this has probably been fear of the relatively narrower range of safety of drugs in children in the absence of a specific dosage scale (ml. mixed pentothal–curare per lb. body wt.) for specific anaesthetic purposes (e.g., ml. of the mixture for orotracheal intubation). Each is usually given alone in small and uncertain quantities (31) generally as adjuvants to the other anaesthetic agents. Volpitto (34) reported the intubation of children after rapid induction with mixed pentothal–curare but his initial doses were insufficient to eliminate the danger of hypoxia from laryngeal closure. It was found that additional amounts were generally needed and periods up to ten minutes were apt to elapse from initial injection to intubation. His range of dosage was too indefinite to provide the safety of predictable results. On the other hand the use of cyclopropane, the only other powerful and relatively non-toxic general anaesthetic agent, is largely restricted especially in infants and small children by the resistance and the heat and water retention of closed systems and by the questionable reliability of complete carbon dioxide removal by soda-lime (2). Ethyl ether has thus remained the chief and in most places the only paediatric general anaesthetic agent regardless of its poisonous effects on the unstable metabolic balances of children. There exists, therefore, a definite need in paediatric anaesthesia for the advantages provided by rapid intubation and maintenance with mixed pentothal–curare–nitrous oxide in adults. It was therefore decided to study this technique in the oldest children and gradually extend it as far down the paediatric age scale as possible with safety in an attempt to find a safe and relatively accurate scale of dosage of mixed pentothal–curare for rapid intubation and possibly maintenance.

At first, especially in some of the older children (10–14 yr. of age), different proportions of pentothal with curare were tried but it at once became apparent that the optimum mixture for children was the same as for adults (1). The amount of this pentothal–curare mixture needed for intubation of 100 lb. children (apparent age 14 yr.) when rapidly injected was expressed in ml./lb. body wt. and used to approximate the preliminary rapid intubation dose for 90 lb. children (app. age 13 yr.) and so on down the weight-age scale. This preliminary clinical investigation was carried out through 90 operations requiring orotracheal intubation and/or abdominal relaxation in the patients ranging from 14 years of age almost to the newborn. A tolerance to an intubation dose of pentothal–curare relatively equivalent to that of adults and to subsequent maintenance doses equivalent to one-half that of adults was exhibited by all ages down to infants 1 year old (20 lb.). As the investigation proceeded it became increasingly apparent that the minimum or optimum amount of rapidly injected pentothal–

curare required for intubation was so closely related to body weight in children that it can be accurately and safely predicted. The usual technique of rapid intubation and maintenance with pentothal–curare–nitrous oxide in adults was, after a few additions and minor changes, made perfectly adaptable to children and infants.

Preliminary Considerations

The indications, contra-indications, and possible complications of this technique in adults were used initially and in accordance with paediatric principles to govern rejection and conduct of cases. Further modifications and additions were made from the information gained in the investigation. The limited number of cases, however, requires that the findings be looked upon as provisional rather than proven. Most important of all, however, is the warning that it is equally as safe and in special cases actually safer (*vide infra*) than the other methods only in the hands of a fully trained, skilled, and knowledgeable anaesthetist providing adequate ventilation from the onset to recovery.

Indications

By the end of this investigation the impression was quite definite that this technique of rapid intubation and of maintenance with pentothal–curare–nitrous oxide was superior to all the other types of anaesthesia for orotracheal intubation and/or abdominal surgery in children and in infants over 20 lb. It provides better operative conditions (quieter respiration, smoother relaxation, and less oozing), less disturbances in paediatric physiology and biochemistry, and more rapid recovery to complete normality.

(A) Conditions in the Patient

(1) Toxic states such as fever, acidosis, uraemia, dehydration, toxaemia, and electrolyte imbalance as seen in intestinal obstruction, infections, burns, renal disease, diabetes, etc.

(2) Conditions requiring rapid induction and intubation for immediate seizure of control of the air passages.

(*a*) Fluids or food in the stomach.

(*b*) Passable* partial obstruction of the upper respiratory tract before or during induction. This includes such conditions as very swollen tonsils, copious secretions, persistent laryngeal stridor which would not preclude good pulmonary oxygenation with pure oxygen before induction, may cause serious respiratory hypoxia during slow induction, but would not prevent direct laryngoscopy and intubation of the relaxed patient.

(B) Nature of the Operation

With the exception of neurosurgery and thoracic surgery this technique of anaesthesia was employed in infants and children for operations representative of practically every type and site of surgery requiring intubation and/or re-

*In contrast to "impassable" conditions such as fixed flexion of the head, ankylosis of mandible, etc. which prevent direct laryngoscopy and/or intubation of the relaxed patient.

laxation. To illustrate this range a few typical examples and ages of this series of cases are listed.

The duration of these operations varied from 30 minutes to 4 hours. This method of pentothal–curare–nitrous oxide anaesthesia was especially advantageous over other methods for the following types of procedures in children.

TABLE I

Operation	Age of Patient	Operation	Age of Patient
Tonsils and adenoids	14 years	Colostomy closure	9 years
Tonsils and adenoids	6 years	Intussusception	18 months
Tonsils and adenoids	18 months	Laparotomy (nephritis with temp. 102°)	5 years
Hair lip repair	6 months	Incarcerated inguinal hernia	8 months
Radical mastoid	10 months	Appendectomy	5 years
Bronchoscopy	4 years	Orthopedic limb surgery	Where the position of the patient or other factors made intubation necessary
Oesophagoscopy	2 years	Lengthy skin graftings	
Laparotomy (acute pancreatitis without shock)	5 years		

(1) Short procedures requiring intubation and only 15 to 45 minutes, such as tonsillectomy, are simply managed by a single intubating dose of pentothal–curare in what is later referred to as the "single shot technique."
(2) Peroral endoscopic procedures that are expected to last well over 10 minutes.
(3) Abdominal operations, especially if the patient is systemically ill.
(4) Major surgery with cautery.
(5) Lengthy operations especially in infants and younger children. The use of pentothal–curare for intubation and then for maintenance even of only the first half of 2- to 5-hour operations greatly reduces the amount of other agents and their adverse effects.

There was no paediatric neurosurgery or thoracic surgery available at the time for this investigation. However, I have since used this technique for both types of surgery in small children with all of the advantages obtained in adults.

(C) Anaesthetic Advantages

(1) The various degrees of hypoxia and/or hypercarbia that usually accompany induction and intubation by other methods and agents especially in children are eliminated by this technique (19). The sudden and profound relaxation of the jaw and larynx prevents laryngospasm and allows the immediate institution of adequate respiration (controlled).
(2) Barbiturate–relaxant–nitrous oxide is the only safe general anaesthetic for major paediatric surgery that is entirely free from the hazard of explosions in operating rooms and equipment not completely explosion-proofed.
(3) Rapid intubation allows the surgical preparation of the patient to begin 90 seconds after the insertion of the needle of induction. This is particularly welcome in over-crowded operating schedules and for short procedures

such as tonsillectomies where the time ordinarily needed for induction and intubation may approach that required for the surgery.

(4) The duration of emergence (end of operation until children opened their eyes on command or infants cried or otherwise reacted to a painful stimulus) averaged approximately 3 to 5 minutes—as short as emergence from cyclopropane and shorter than from ether. It was unaccompanied by the laryngospastic tendencies and the postoperative nausea and vomiting which are frequent when ether and cyclopropane are used.

(5) The intravenous puncture for injection encourages the use of intravenous fluids in infants and children.

(6) Each of the other major paediatric general anaesthetic agents has at least one specific and formidable drawback that is relatively absent from pentothal–curare–nitrous oxide in infants and children; e.g., the phosphoric acidosis (5, 28) and other adverse biochemical effects (12, 29) of ether may reach dangerous proportions especially in predisposed children (21, 33).

Contraindications

(A) Conditions in the Patient

(1) Hypoxia of any type and cause not completely relieved by oxygen and/or other measures before induction.

(2) Even the *possibility* of "impassable" conditions of the respiratory tract, i.e. where immediate intubation and control of respiration of a relaxed patient cannot be guaranteed.

(3) Shock in any degree.

(4) In progressively smaller infants (20 lb. and down) pentothal hypnosis increased considerably in duration (rather than depth). On the other hand the effects of curare lengthened only slightly. The duration of light pentothal hypnosis from the time of administration of an intubation dose of the pentothal–curare mixture was approximately ¾ hour in 20 lb. (12 mo.), 1 hour in 15 lb. (6 mo.), and 1½ hours in 7 lb. (newborn) infants. The addition of any further amounts (maintenance doses) of the mixture increased considerably these durations of hypnosis. As a result the first patients remained asleep (but could be roused) for up to three hours postoperatively. In subsequent cases this was avoided and rapid emergence to normality was attained by restricting the use of this technique in small infants to operations with an expected duration of at least twice that of the expected hypnosis from an intubating dose. No further pentothal–curare mixture was given except in very long operations (3–5 hr.) where one or two maintenance doses were used before going on to ether. The amount of ether needed to maintain these patients was quite small. The smaller the infant the longer the persistence of the pentothal and thus the less the amount of ether needed for maintenance. Hence the seemingly paradoxical statement that the longer the operation and the younger the infant the greater the benefit (ether-sparing effect) of pentothal–curare. Shorter operations in infants under 6 months may be

better managed by intubation prior to injection and then giving just enough pentothal–curare for surgery.

(5) Miscellaneous conditions such as wet lungs, bronchial asthma or related allergies, liver damage especially in infants, and the absence of available veins coupled with no indications for an intravenous cut-down.

(B) Nature of the Operation

This technique is impractical in paediatric operations not requiring intubation or abdominal relaxation, and in ultra-short procedures (less than 15 min.) in children or procedures of less than 1–1½ hours in infants. Surgery of the orbit, side of the neck, or of the larynx may cause autonomic reflexes of sufficient intensity to make cardiac arrest possible. In two cases, a resection and recession operation in a child aged 6 years and a congenital torticollis in a child aged 7, the patients were intubated under this pentothal–curare–nitrous oxide technique and carried in plane 1 anaesthesia. In both, the onset of surgery was accompanied by pronounced arrhythmias of the pulse regardless of good atropinization and oxygenation. Regular ventricular rhythm was only re-established by deepening the anaesthesia to mid-plane 2 by the addition of ether.

(C) Anaesthetic Contraindications and Disadvantages

(1) Rapid induction–intubation of infants and children with pentothal–curare would certainly be as dangerous in the hands of the uninitiated or inexperienced as it is safe and advantageous when under the control of the competent anaesthetist with experience in paediatric anaesthesia.

(2) Failure to have first-class equipment in proven working order and all of it immediately at hand.

(3) The almost simultaneous administration of agents intravenously and by mask requires the presence of an assistant to manage either the mask or the venipuncture. However, once the technique has been so learned as to be nearly automatic one anaesthetist can manage it alone except in difficult cases.

(4) Blind nasal intubation is rendered difficult or unsuccessful by the absence of spontaneous respiration.

(5) Surgeons are easily frightened by the sudden disappearance of spontaneous breathing even though it is at once replaced by adequate controlled respiration.

Almost all of these anaesthetic disadvantages can be easily circumvented.

Possible Complications

There were no complications of note in this series and at no time was a patient in trouble. The following effects or "minor complications" were harmless and mostly mild and transient.

1. Pulse changes. A few seconds after rapid injection of the intubating dose there occurred a palpable moderate decrease in pulse rate and strength lasting 2 to 5 seconds in about one-quarter of the cases tested. No irregularities were felt. Laryngoscopy and intubation caused a moderate increase in pulse rate and strength in about one-half of the cases and occasionally a palpable transitory

irregularity. The tendency of intubation to reverse the pulse effects of rapid injection back to normal was noticed.

2. Blood pressure changes were measured sphygmomanometrically in only a few cases and in approximately two-thirds of these a transient fall of 5–15 mm. of mercury in systolic pressure and a lesser amount in diastolic pressure was noted. Intubation was prone to cause a quick return to normal. The colour of all the patients was normal or somewhat paler than normal from rapid injection to intubation.

3. Respiratory changes. If the intubating dose of pentothal–curare was not given rapidly or was less than the required amount or if intubation was attempted before 30 seconds or later than 90 seconds after injection, the cords were liable to be mobile with a tendency to weak but bothersome closure on laryngoscopy. Intubation without first injecting a small extra amount of pentothal–curare in these cases would almost invariably result in a spastic thorax ("bronchospasm") or moderate bucking on the tube. *Postoperative respiratory depression* lasting more than 3 minutes was not common, but invariably the result of giving more pentothal–curare too near the end of an operation. Easy management of it by assisted respiration with oxygen made it a matter of no particular concern. On the other hand, its *neglect would be lethal and inexcusable.* Excessive respiratory tract secretions were uncommon and due to lack of atropinization, food or fluids in the stomach, or the presence of respiratory infection.

4. Prolonged postoperative hypnosis occurred only in the first of the small infants in this series and was due to overdosage of pentothal relative to their lesser ability to destroy it. These patients remained asleep for up to 3 hours but could be roused and had no overt respiratory depression.

5. Perivascular injection happened in one case as a result of reflex movement of the limb not being held firmly enough. The possibility of delayed respiratory depression from later absorption was kept in mind but the amount was apparently insufficient.

It would be more accurate to refer to these minor complications as "potential avenues to serious complications." The possible serious complications of this technique in children would likely be similar to those resulting from injudicious use and management of it in adults. These are cardiac arrest, "pentothal shock," respiratory anoxia, prolonged deep depression, and limb damage from intra-arterial or perivascular injection. The causes of these are well known and obviously avoidable.

Currently, the most controversial objection to rapid injection and intubation with barbiturate–relaxant anaesthesia is the possibility of cardiac arrest. In this method of anaesthesia in adults, disturbances in cardiac conduction commonly occur at any of four points: (i) during the transient wave of depression (deep anaesthesia) from the rapid injection (10, 30); (ii) laryngoscopy and intubation (8, 10, 25); (iii) surgical stimulation of cardiac reflex receptor areas (8); and (iv) endotracheal suction and extubation (11). Except for one (30) that may have been due to the rapid injection itself, no cases of cardiac arrest from this cause could be found in the literature. In fact Colon-Yordon *et al.* (10) as well

as Converse *et al.* (11) employed rapid barbiturate–relaxant injection for intubation of over a thousand cases of cardiac and cardiovascular disease of almost every type and there were no cardiac stoppages. The underlying causes of cardiac disturbances and of arrest under light general anaesthesia are well known (8, 9, 25, 35) and avoidable. The main aggravating factor is hypoxia. However, Krumperman *et al.* (19) showed that properly managed rapid injection and intubation produce very little alteration in blood oxygen and carbon dioxide compared to that produced by other methods such as ether induction. Furthermore, light anaesthesia for intubation is avoided by performing it within 30 to 60 seconds after rapid injection, i.e., before the transient wave of deep anaesthesia had thinned out by redistribution to plane 1. Finally, the important thing is an awareness that transient electrocardiographic disturbances are not uncommon in any type of general anaesthesia and that during light anaesthesia the existence of one or more aggravating factors can magnify these disturbances to a cardiac arrest. On the other hand deep anaesthesia itself can cause cardiac depression and arrest. Dripps *et al.* (18) nicely sum up this situation in their statements: "However, overzealous use of deep general anesthesia or cardiac depressant drugs in an attempt to prevent reflex circulatory alterations caused by intubation ultimately may be more detrimental to the patient than the condition that was to be avoided," and "The physician must never lose sight of the fact that catastrophies at the time of intubation are more likely to ensue from anoxia, overanesthetization or reactions to topical anesthesia than from circulatory reflexes incurred by facile intubation."

Preoperative Preparation

The technique and dosages to be given here were evolved and are based on the following preparations.

(*a*) Preoperative examination which included taking the exact current weight, haemoglobin, and a sharp lookout for contra-indications.

(*b*) Premedication which consisted of combined nembutal, morphine, and hyoscine according to the tables of Leigh and Belton (20).

(*c*) Outlay of equipment as follows:

1. Source and delivery of anaesthetic agents from an anaesthetic machine with single line delivery (of at least oxygen, nitrous oxide, and ether), masks with bags of appropriate sizes (29), a Stephen-Slater non-rebreathing valve (32) with a reservoir bag attached, and a syringe loaded with the calculated required amount of the pentothal–curare mixture.

The most suitable syringes for holding and measuring calculated total dosage while providing a scale fine enough for fractional maintenance doses were 20, 10, and 2 ml. sizes for patients weighing over 50 lb., 10 to 50 lb., and under 10 lb. respectively. The amount of the mixed pentothal–curare solution drawn up in readiness for a given case was one of

(i) The calculated intubation dose (approx. lb. body wt./6) plus a small amount extra (about 1/5 of intubation dose), for "single shot" procedures.

(ii) Twice the calculated intubating dose (lb. wt./3) for longer operations.

2. Intravenous equipment including short or medium bevelled needles (21, 20 and 19 G.) for venipuncture, arm or leg splints, and, if necessary, a venous cut-down set.
3. Intubation equipment including carefully sized endotracheal tubes with connectors to fit the Stephen-Slater valve.
4. Maintenance material such as a pressure cuff, suction catheters, etc.

An assistant should be available if not actually helping in this technique. Just before induction the operating table should be put in slight Trendelenburg position to counteract the transient decrease in blood pressure that generally follows the rapid injection of pentothal (30).

Technique and Dosage

The technique and dosage for rapid injection of mixed pentothal–curare for intubation and subsequent maintenance of anaesthesia in infants and children as developed in this series of cases is presented hereunder as four consecutive phases.

I. Preliminary induction for venipuncture
II. Injection and dosages for intubation
III. Maintenance
IV. Extubation and emergence.

I. PRELIMINARY INDUCTION FOR VENIPUNCTURE

The child is induced carefully and smoothly by open mask insufflation with nitrous oxide (10 litres per min.) which becomes partial rebreathing or non-rebreathing (and the nitrous oxide flow is cut to 4–6 l./min.) when the mask is finally brought in contact with the face. The moment the child exhibits slight duskiness (nails or lips) oxygen is turned on to at least 20 per cent of the total flow and the skin analgesia and light hypnosis thus maintained with oxygen–nitrous oxide. A limb is selected, taped to a splint, and the intravenous puncture or procaine infiltration and intravenous cut-down is performed. If 80 per cent nitrous oxide is not sufficient to "hold" the child through this, a trace of trichlorethylene is added and the nitrous oxide reduced to 70 per cent. In special cases such as respiratory hypoxia or cardiac conditions where a high oxygen flow is necessary, nitrous oxide is contra-indicated for this phase, the venipuncture or cut-down being performed under local anaesthesia during pure oxygen alone or with a trace of trichlorethylene or ether.

II. INJECTION AND DOSAGES FOR INTUBATION

The moment the needle is in place in the vein any subsidiary agent in use (trichlorethylene or others) is at once turned off. The percentage of oxygen is increased to 50 per cent (25–100 per cent) of the total flow in order to eliminate even the possibility of any hypoxia during the sudden onset of the effects of pentothal. In this regard, it is also preferable that the injection of pentothal–curare be timed so that the child shall have taken about seven breaths of the higher oxygen flow (i.e., coefficient of ventilation (4)) before the onset of the anaesthesia. The intubating dose of pentothal–curare is injected right after venipuncture. The intubation dosages of mixed pentothal–curare for the whole

weight or age range of children and infants as found and computed from this series of cases are presented in Table II.

In the average child with average effects from this premedication the minimum intubating dose will barely allow intubation, and active bucking on the tube will usually ensue. On the other hand the maximum necessary intubating dose

TABLE II

Wt. (lb.)	App. age (yr.)	Intubating dose (ml. pent.–curare) min.	opt.	max.	Wt. (lb.)	App. age (mo.)	Intubating dose (ml. pent.–curare) min.	opt.	max.
100	14	15.0	16.0	17.0	20	12	3.0	3.4	3.8
90	13	14.0	15.0	16.0	19	11	3.0	3.2	3.4
80	12	13.0	14.0	15.0	18	10	2.8	3.0	3.2
70	11	11.0	12.0	13.0	17	9	2.6	2.8	3.0
65	10	10.0	11.0	12.0	16	8	2.4	2.6	2.8
60	9	9.0	10.0	11.0	15	6	2.3	2.5	2.7
55	8	8.0	9.0	10.0	14	4	2.2	2.4	2.6
50	7	7.0	8.0	9.0	13	3½	2.0	2.2	2.4
45	6	6.5	8.0	8.5	12	3	1.8	2.0	2.2
40	5	6.0	7.0	8.0	11	2½	1.6	1.8	2.0
35	4	5.0	6.0	7.0	10	2	1.4	1.6	1.8
30	3	4.0	5.0	6.0	9	1½	1.2	1.4	1.6
28	2½	3.8	4.5	5.0	8	1	1.0	1.2	1.4
26	2	3.6	4.0	4.4	7	Birth		1.0?	
24	1½	3.4	3.8	4.2	6				
20	1	3.0	3.4	3.8	5	Prem.		0.5?	

will usually produce somewhat more anaesthesia and relaxation than necessary but no untoward effects. The minimum dose is approximately one-tenth less and the maximum necessary dose about one-tenth more than the optimum intubating dose. In a few cases, dosages one-third greater than the optimum dose were given rapidly with no apparent harm to the child.

The *optimum rapid intubating dose* of mixed pentothal–curare is (see Table II) very close to 1 ml. per 6 lb. body weight for all children. This amounts to 0.125 mg. (0.8 units) of curare and 4 mg. of pentothal per lb. body weight or 5 units curare and 25 mg. pentothal per 6 lb. body weight. The optimum dose permitted easy intubation usually without subsequent bucking and was employed in all cases except where a minimum or maximum dose was indicated. Relative indications for a minimum or maximum intubating dose are as listed in Table III.

The calculated intubating dose is injected at a rate of about 0.5 to 1.0 ml./sec. The needle is then left in the vein and the syringe taped to the limb at least until after intubation is completed. Cases with reduced cardiac reserve or output or with serious ECG disturbances and all infants should probably be injected more slowly.

The onset of pentothal anaesthesia occurs about 5 to 10 seconds after the *start* of the injection (decholin arm-to-tongue circulation time is 10–15 sec. in adults) and is marked by sudden apnoea which may be heralded by a deep

TABLE III

	Relative indications	For min. dose	For max. dose*
1.	Patient near either end of weight and age scale	Tiny infants (under 3 mo.)	Largest children (over 11 yrs.)
2.	Considerable disparity between chronological (real) and apparent (wt.) age	Chronological age two or more steps below apparent age	Chronological age two or more steps more than apparent age
3.	Health, tone and resistance	Poor, as from deranged metabolism, long stay in bed, etc.	Several previous anaesthetics
4.	Physique beyond average	Asthenic	Very robust
5.	Premedication effects	Depressed	Wide awake
6.	Duration of surgery	Very short	Long
7.	Speed of injection		Slower than rapid

N.B.: When in any doubt use the larger intubating dose.

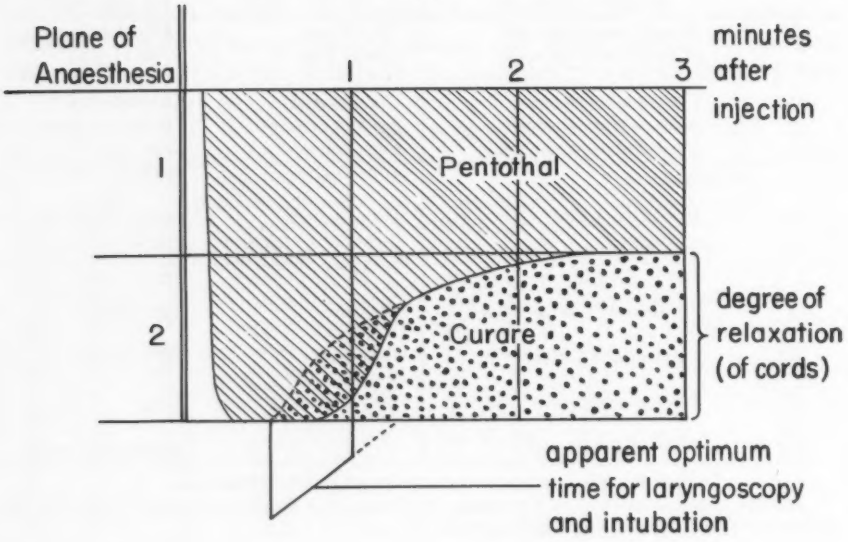
*Refers to the usual maximum necessary intubating dose which is not nearly as large as the maximum tolerated intubating dose would be.

respiration or two, and by sudden disappearance of lid reflexes and eye movement. A closed mask with partial or non-rebreathing bag attached is applied and manually held to the child's face and adequate or more than adequate controlled respiration with 50 per cent (25–100 per cent) oxygen in nitrous oxide begun at once. The intermittent positive pressures on the bag should be kept low (rapid and shallow) to avoid inflating the stomach. This respiration is continued right up to the initiation of laryngoscopy in order to ensure abundant pulmonary oxygen and absence of hypercarbia throughout intubation.

The optimum time for laryngoscopy and intubation seemed to be 30 to 60 seconds after injection. Laryngeal instrumentation before or after this period was very liable to result in cord closure on laryngoscopy and/or a short period of mild bucking after intubation. Early intubation (30 sec.) under the initial wave of deeper anaesthesia was favoured over later intubation (60 sec. or more) under lightening anaesthesia. The tendency of laryngeal manipulation to end the transient hypotension of rapid barbiturate induction (30) is invoked earlier, and the objections raised against laryngoscopy and intubation under very light anaesthesia are obviated. A rough approximation of the early depths of pentothal anaesthesia and the onset of curare effects on the larynx as observed clinically are shown in Figure 1.

At the time selected for intubation, controlled respiration is stopped and the mask discarded from the patient's face. Laryngoscopy and intubation are immediately carried out, smoothly and quickly. In most of the patients that had received an adequate intubation dose, the vocal cords were in the cadaveric position and showed little or no motility. Mild adduction of the cords did not

FIGURE 1



interfere with intubation, the cords being gently and readily separated by the endotracheal tube. As soon as the endotracheal tube is in, it is connected to the Stephen-Slater valve and reservoir bag and controlled respiration with nitrous oxide–oxygen is continued. If intubation is followed by more than a brief period of bucking or tight chest (so-called "bronchospasm") an additional dose (¼ of intubating dose) of the mixture is given. In about 10 per cent of cases the cords closed on laryngoscopic exposure and did not reopen during a waiting period of 10 seconds. In these the laryngoscope was removed without attempting intubation, the mask was reapplied and controlled respiration was continued for 30 seconds after the injection of an extra dose (approx. ¼ of intubating dose) of the mixture. Laryngoscopy and intubation were then carried out. It was felt that many of these patients exhibited laryngeal reddening (hyperirritability) and/or had not received an adequate intubating dose in the first place. In the "single shot technique" for short procedures such as tonsillectomies the needle (and syringe) is now removed from the vein. Otherwise the syringe is taped to the limb or connected to the intravenous drip for maintenance of anaesthesia by intermittent doses.

The average duration of respiratory paralysis, relaxation, and anaesthesia in children following the rapid injection of an intubating dose of pentothal–curare and under maintenance with controlled or assisted respirations with 30 per cent oxygen and 70 per cent nitrous oxide is given in rough approximation in Table IV.

TABLE IV

Minutes after injection	Respiration	Relaxation	Plane of anaesthesia
0	apnoea	++++	2 to 1
3	returning	++	lower 1
10	subnormal	++	mid 1
20	normal	+	upper 1
25	normal	nil	signs of emergence
30	Bucking occurs if the tube is not removed or further anaesthesia is not added. Extubation and administration of pure oxygen result in active thalamic response to pain.		
35	eyes open on command.		

NOTE: Duration of pentothal anaesthesia is longer in infants under 20 lb.

III. MAINTENANCE

(*a*) *Of respiration.* This must be assisted or controlled continuously with at least 20–30 per cent oxygen in an adequate rate of total gaseous flow (27) from a non-resistant non-rebreathing system.

(*b*) *Of anaesthesia and relaxation.* Depending especially on the type and requirements of the surgery most of the patients were carried for 10 to 30 minutes after intubation before supplementary anaesthesia was needed. In abdominal surgery a supplemental or "maintenance" dose of pentothal–curare was needed before opening the peritoneum.

In short (¼–¾ hr.) non-abdominal procedures such as the removal of adenoids and tonsils a "single shot" (the intubation dosage) was all the anaesthesia necessary in addition to the nitrous oxide. On insertion of the endotracheal tube the needle was removed, the child's arms were abducted to the sides and the operation was begun at once. If excessive lightening occurred before the end of the operation, anaesthesia and relaxation were readily "stretched out" for an extra 5 to 15 minutes merely by adding a trace of ether or trichlorethylene to the nitrous oxide and oxygen mixture. The signs of insufficient anaesthesia and relaxation indicating the need for maintenance doses were similar to those in adults. The agents used to maintain first plane anaesthesia and the required degree of relaxation subsequent to that of the intubation dose of pentothal–curare were pentothal–curare–nitrous oxide alone or supplemented by ether or trichlorethylene, or ether or trichlorethylene alone.

Pentothal–curare–nitrous oxide was generally used as the sole maintenance combination in all of the cases until partial or complete changeover to inhalation agents became desirable. While continuing to administer nitrous oxide and oxygen throughout the operation, a maintenance dose of mixed pentothal–curare was injected whenever indicated by the onset of signs of lightening. The optimum

intermittent maintenance dose was found to be $\frac{1}{10}$ to $\frac{1}{5}$ the original intubating dose. The smaller dose ($\frac{1}{10}$) was favoured in infants, near the end of operations or in the presence of supplementation with a trace of one of the other anaesthetic agents. The larger dose ($\frac{1}{5}$) was favoured in older children, in the early phases especially of long operations or where the signs of lightening were pronounced. The interval between doses averaged 20 to 30 minutes, with progressive lengthening between successive doses especially in infants. The average amount of pentothal–curare needed to maintain plane 1 anaesthesia and adequate relaxation for the longer operations is depicted in Table V.

TABLE V

Duration of operation	Maximum required maintenance dose (expressed as fraction of intubating dose)	
	Children	Infants
2 hours	$\frac{1}{2}$	$\frac{1}{4}$
4 hours	1	$\frac{1}{2}$

The maximum amount of pentothal–curare that could be safely administered or in other words the tolerance limit to pentothal in any given case was assumed to have been reached with the advent of any one or more of the following signs:

(i) Downward trend in blood pressure not due to some other cause such as deep anaesthesia or the bradycardia of insufficient atropinization.

(ii) Increasing or excessive respiratory tract secretions.

(iii) When the sum of the maintenance doses equalled the intubating dosage in children or one-half of the intubating dose in infants.

The maximum tolerated amount of pentothal–curare was reached in but a few cases because only an occasional operation is of sufficient duration to need it. The course of anaesthesia was smooth and free of metabolic disturbances or the effects of deep anaesthesia. Postoperative recovery and emergence, however, was liable to be slow ($\frac{1}{2}$ hr. or so) unless the last maintenance dose of pentothal–curare was given over $\frac{1}{2}$ to 1 hour before the end of surgery. In order to avoid this problem the maintenance dosage of pentothal–curare was considerably reduced by the supplementary addition of an inhalation agent for the latter half and/or especially during the withdrawal phase of operations.

At some point between intubation and the end of surgery it was usually found advantageous and occasionally necessary to reduce or discontinue further pentothal–curare with a partial or complete changeover to ether, trichlorethylene, or cyclopropane. The introduction of the other agent(s) must be cautious and gradual beginning with a trace and then a slow increase of the concentration only as indicated by signs of lightening as the pentothal–curare wears thin. A constant observation and important advantage was the relatively great prolongation of light anaesthesia and relaxation, up to one hour after the last dose of pentothal–curare, that could be obtained from only a trace or small concentration ("subtoxic dose") of ether or trichlorethylene added to the oxygen–nitrous oxide flow. From experience in this series the following conditions appeared

advantageous or as definite indications for partial and occasionally complete supplementations with an inhalation agent:

(i) To "stretch out" anaesthesia in those operations that extend beyond the time provided by the intubating dose of pentothal–curare in the "single shot" technique for short operations.

(ii) In all cases where maintenance with pentothal–curare alone is not specifically desired or where the use of the inhalation agents is not contraindicated, the maintenance dosage of pentothal–curare can be kept well below the maximum and rapid emergence facilitated far out of proportion to the relatively small amount of inhalation agent(s) added. Partial supplementation with a trace of ether or trichlorethylene was therefore begun shortly after intubation in short or medium length operations especially in infants and young children and at about the midpoint of long operations.

(iii) Pentothal–curare maintenance should be discontinued altogether in favour of partial leading to complete supplementation with an inhalation agent ¾, 1, 1½, and 2 hours before the end of surgery in children, 20 lb. infants, 15 lb. infants and 7 lb. infants respectively in order to avoid delayed emergence and residual light pentothal hypnosis in the postoperative period. In long operations pentothal–curare maintenance must be discontinued before this if the maximum tolerated dose is reached. Even where the resultant duration of complete supplementation was considerable, the sparing effect by the previous pentothal–curare was decidedly manifest in the smooth and immediate postoperative emergence and relative absence of disturbed metabolism.

(iv) Where a rich oxygen flow is desired the reduction or discontinuation of nitrous oxide and its analgesia requires substitution with a trace of inhalation agent (or else small maintenance doses of Demerol) to avoid an increasing pentothal–curare demand.

(*c*) *Of colour, pulse and blood pressure.* Throughout maintenance with pentothal–curare–nitrous oxide alone or supplemented by a small amount of another agent the face seemed to exhibit a slight paleness but the colour of the lips, nails, and soles of the feet remained normal. The regular and well-filled pulse maintained at an even 80(80–90)/min. was a welcome contrast to the usual ether pulse. The blood pressure remained a steady normal or low normal, thus imposing a lesser cardiac load than the usually elevated pressure from ether or cyclopropane anaesthesia.

(*d*) *Of drug, fluid, and electrolyte needs.* Maintenance of basal atropinization and analgesia with an occasional small intravenous dose of atropine and Demerol was carried out where indicated. A very small supplementary dose of curare was added near the end of an occasional abdominal case to maintain relaxation while lightening anaesthesia toward emergence. Fluids and electrolytes were given as required.

IV. EXTUBATION AND EMERGENCE

All agents except nitrous oxide and oxygen were tapered to a minimum or discontinued entirely at the earliest moment allowed by the surgical procedure in order to secure definite signs of lightening during the last few skin sutures.

The concentration of nitrous oxide was increased to 80 per cent to substitute for the dwindling amounts of the other agents in maintenance of this early reactive level of anaesthesia. Unexpected signs of excessive reactivity such as a tendency to buck on the tube were controlled by immediate introduction of a moderate concentration of ether with shallow and rapid rather than deep and slow bag pressures.

The rare cardiac arrest (24, 26) from suction and extubation under light anaesthesia is due to aggravation of the reflex electrocardiographic disturbances (11) by hypoxia (17), hypercarbia, roughness, etc. as during intubation. The following procedure of suction and extubation in four serial steps is used to eliminate or safely minimize these factors and thus obviate cardiac arrest.

1. The nitrous oxide is turned off, replaced with pure oxygen (6 l./min.), and the lungs are inflated at least seven times. If the patient showed signs of bucking on the tube, inflations were done rapidly and the third step begun at once. On the other hand, if little or no signs of lightening were present these inflations were carried out at a rate of about seven per minute until the signs were definite.

2. Oropharyngeal suction is performed with a good-sized rubber catheter, which is then replaced on the suction line by a catheter considerably smaller than the endotracheal tube.

3. The Stephen-Slater valve is removed and while suction is pinched off the catheter is quickly inserted down the endotracheal tube into the right main bronchus. At the moment suction is allowed to continue the endotracheal tube and after-coming catheter are gently withdrawn in a single movement requiring 1 to 2 seconds.

4. A mask is applied to the face and the lungs are immediately inflated several times with pure oxygen. The occasional but mild and transient laryngeal spasm was easily overcome with oxygen under positive pressure. Awakening and deeper breathing are hastened by pain stimuli. If necessary these inflations are continued at about only three or four per minute to allow some carbon dioxide build-up until breathing is adequate and the child emergent (opens eyes on command and/or phonates and moves limbs considerably on painful stimulation). Only then is a child considered ready to leave the operating room.

The smoothness and rapidity of extubation and emergence are increased considerably as experience is gained. The ideal objective seemed to be a state of light and rapidly waning anaesthesia permitting oxygenation, suction, and extubation without bucking as the last skin suture is inserted, and followed by emergence to or near a state of wakefulness with adequate breathing within 3 minutes after extubation. This was achieved in about 50 per cent of the cases in each of the age groups, with about one-half of these patients being almost fully awake one minute after extubation. Owing mainly to inexperience in the earlier cases of each age group, the remaining 50 per cent of patients either emerged too quickly and bucked on the endotracheal tube or emerged too slowly and required assisted respiration with oxygen for 3 to 15 minutes after extubation before sufficient breathing and consciousness had returned.

The colour and pulse of every patient remained normal throughout and there

were no cardiac stoppages. Patients left the operating room only when they could be roused (emergent) and were breathing adequately.

Postoperative Observation and Care

The final and a very important margin of safety is provided by sending every case to a fully equipped recovery room or its equivalent for a period of close and expert nursing surveillance. Since delayed and potentially serious postoperative depression from both pentothal and curare has been reported in adults, it was felt that all patients including even those wide awake shortly after extubation should be kept here for a minimum of ½ hour for older children and 1 hour for infants. As an added precaution or guard, tiny infants were usually placed in an oxygen tent especially after major surgery or peroral endoscopy. The slightest sign of deterioration of respiration or colour would of course call for immediate attention to the airway and the administration of oxygen, preferably by assisted respiration from a bag and mask, through the depressed phase. Although there were no cases of delayed or prolonged depression requiring respiratory assistance in this series, Noble (22) reports one child with prolonged curare paralysis following this technique. Adequate artificial respiration resulted in an uneventful recovery whereas postoperative neglect would have resulted in an unnecessary fatality.

After reaching the recovery room nearly all patients not previously awake could be roused to wakefulness within 10 or 15 minutes. If left undisturbed the majority, especially the younger ones, lapsed into a light "normal" sleep lasting 30 to 60 minutes, from which they awoke quietly and refreshed. The normal colour, pulse, and respiration throughout the recovery period contrasted sharply with the flushed appearance, rapid pulse, and acidotic breathing after ordinary ether anaesthesia. There was no vomiting and very little postoperative restlessness except where a sizable amount of ether had been used for maintenance. Restlessness was otherwise usually due to pain and easily controlled with a very small intramuscular dose of Demerol. There were no laryngospastic episodes, atelectasis, or other postoperative complications. Preoperative systematic illness such as fever, acidosis, etc. appeared very definitely improved on emergence. The nursing and other personnel concerned felt that recovery time and troubles (but not responsibility!) were considerably less than with other types of paediatric anaesthesia.

Summary

Some of the advantages of mixed pentothal–curare (Baird's solution) and nitrous oxide anaesthesia over the other types of general anaesthesia in adults are noted and the need in paediatric anaesthesia for a method with similar advantages was pointed out. The main object of this preliminary investigation was to seek a basic dosage scale of mixed pentothal–curare (ml./lb. body wt.) in children for a specific purpose (rapid injection for orotracheal intubation) so that this technique of anaesthesia and its advantages might be extended into the paediatric field. A surprisingly constant and accurate scale was found, and so it was possible to modify the well-known rapid injection technique for advantageous use in children and infants.

The indications, contra-indications, and possible complications of this method in children were assumed to be basically similar to those in adults and those found to differ significantly from experience with adults or felt to be of special importance in paediatric anaesthesia are emphasized. The technique itself is, except for the added preliminary induction phase and quantitative modifications, similar to that employed in adults. It is presented in much detail, however, in order that the clinical effects of each step and the management thereof in children may be fully understood and the margins of safety guarded. Postoperative observation and care are similarly emphasized.

The amounts of pentothal–curare required for rapid intubation and for maintenance of children and infants and the clinical effects thereof were remarkably uniform. The salient findings are as follows:

1. The optimum mixture for 100 lb. children down to about 20 lb. infants is that of Baird's solution (25 mgm. pentothal with 5 units curare per ml. of solution). Since the duration of the effects of pentothal increases and those of curare remain about the same in progressively younger infants, a mixture with a smaller proportion of pentothal (15 or 20 mgm./ml.) would likely be more suitable for them.

2. The tolerance of all of the children and infants to a rapidly injected dose of the pentothal–curare sufficient for intubation was excellent and probably equivalent to that of adults. The tolerance displayed to subsequent total maintenance dosage by 20 to 100 lb. patients appeared to be about one-half that of adults, and by infants under 20 lb. it was probably about one-quarter that of adults.

3. The dose of rapidly injected pentothal–curare needed for intubation was very closely related to body weight and could therefore be predicted with safety and much greater accuracy than in adults. The amount used for maintenance seemed at least as closely related to body weight as in adults.

4. The optimum rapid intubation dose of millilitres of pentothal–curare mixture (1) for children and infants is lb. wt./6, $\pm 1/10$ for variables. The optimum intermittent maintenance dose is about $1/10$ to $1/5$ the intubating dose given every 15 to 30 minutes. The maximum tolerated total maintenance dosage in children seems to be equal to the intubation dose and in infants it is only one-half of the intubating dose.

5. The degree and duration of pentothal–curare anaesthesia and relaxation in children are comparable to those observed in adults.

6. The amount of pentothal–curare needed for maintenance can be greatly reduced by a disproportionately small amount (trace) of ether or trichlorethylene. This was found to be particularly useful near the end of operations in the interests of rapid emergence and in halving the total maintenance dosage of pentothal–curare in lengthy procedures.

Throughout this investigation all of the well-known advantages seen in adults from rapid intubation and maintenance with pentothal–curare–nitrous oxide were obtained. The disadvantages and possible dangers in children are easily circumvented by knowledgeable and careful selection and management.

Comments

Apart from the general dosage scale of pentothal–curare, the findings and observations in the limited number of cases of this investigation must be considered preliminary and provisional until many more cases have been reported, preferably by several investigators. Even the dosage proportions and range may require some revision especially for small infants. Furthermore, various combinations of the other relaxants and short-acting barbiturates could be similarly investigated and employed in paediatric anaesthesia, each of which might more exactly fulfil the particular needs of special cases.

The basic prerequisites for the safe employment of rapid intubation and maintenance with barbiturate–relaxant–nitrous oxide anaesthesia in children and infants are:

(*a*) Management throughout only by those with the knowledge, experience, and expert technical training to handle all of the phases and possible problems.

(*b*) A beginning with older children and then a gradual descent of the paediatric weight-age scale as experience is gained.

(*c*) Adequate assisted or preferably controlled respiration from rapid injection to emergence.

(*d*) Care to avoid overdosage in maintenance especially of long procedures.

(*e*) Expert and careful postoperative care and observation in a well-equipped recovery room or its equivalent.

Neglect of any of these prerequisites could result in fatalities which are apt to be blamed on the inanimate agents themselves rather than on those responsible for their safe administration and management. An example of this is found in a recent statistical survey (3) wherein Beecher focuses the spotlight of blame for anaesthetic deaths on the muscle relaxants. Griffith (13) deftly places his finger on both the real cause and the prevention of such deaths in one sentence, "If Beecher's survey proves anything, I think it proves that there is need for more good anaesthetists, trained to use their brains intelligently, individually and on a level with the exacting standards of good medicine." The results of this investigation are offered in this light and in the hope that children will not have to go on paying the price of ether morbidity for safety in anaesthesia.

Addendum

Since completion of this investigation, the technique described has been employed in over 400 children by Dr. A. B. Noble of Kingston, Ontario, and in a large number of children by Dr. H. M. Slater and associates of Montreal. Appreciation is expressed to Dr. Slater for his valuable advice and criticism.

Résumé

Quelques-uns des avantages d'un mélange de pentothal–curare (Solution de Baird) et de protoxyde d'azote employé en anesthésie sur les autres types d'anesthétiques chez les adultes sont notés et le besoin en pédiatrie d'une méthode anesthésique comportant des avantages semblables est indiqué. Le

but principal de cette enquête préliminaire était l'établissement d'une échelle fondamentale de dosages de pentothal–curare mélangé (cc./lb poids-corps) à l'intention des enfants (injection rapide pour l'intubation orotrachéale) de façon à ce que cette technique d'anesthésie et ses avantages puissent s'appliquer au domaine de la pédiatrie. Une échelle étonnamment constante et précise a été trouvée, et ainsi il a été possible de modifier la technique bien connue d'injection rapide pour l'appliquer avantageusement aux enfants et bébés.

On a présumé que les indications, contre–indications et les complications possibles de cette méthode chez les enfants étaient fondamentalement semblables à celles des adultes. Nous ne présentons que celles qui diffèrent d'une manière significative de l'expérience chez les adultes ou qui semblent offrir une importance spéciale pour l'anesthésie en pédiatrie. La technique elle-même, à l'exception de la phase supplémentaire d'induction préliminaire et des modifications quantitatives, est elle-même identique à celle employée chez les adultes. Elle est présentée cependant en grands détails, pour que les effets cliniques de chaque phase, et le traitement subséquent des enfants soient bien compris et la marge de sécurité bien observée. Les observations et les soins après l'opération sont également soulignés.

Les quantités de pentothal-curare nécessaires pour l'intubation rapide et pour le maintien des enfants et des bébés et les effets cliniques qui en découlent ont été remarquablement uniformes. Les données saillantes sont les suivantes.

1. Le mélange optimum pour les enfants de 100 livres jusqu'aux bébés de 20 livres est celle de la solution de Baird (25 mgm de pentothal avec 5 unités de curare par cc de la solution). Etant donné que la durée des effets du pentothal augmente et que celle du curare reste à peu près la même chez les enfants progressivement plus jeunes, un mélange d'une proportion plus petite de pentothal (15 ou 20 mgm/cc) semblerait être plus convenable dans leur cas.

2. La tolérance de tous les enfants et des bébés à une injection rapide d'une dose de pentothal–curare suffisante pour l'intubation était excellente et probablement équivalente à celle des adultes. La tolérance à des doses totales maintenues par des patients de 20 à 100 livres semblait être environ la moitié de celle des adultes, et celle des bébés en-dessous de 20 livres était probablement un quart environ de celle des adultes.

3. La dose rapidement injectée de pentothal–curare nécessaire à l'intubation était en rapport étroit avec le poids du corps et pouvait être prédite par conséquent avec sécurité et beaucoup plus de précision que chez les adultes. La quantité employée pour la dose d'entretien semblait du moins aussi relative au poids du corps que chez les adultes.

4. La dose optima en centimètres cubes de solution de pentothal–curare nécessaire à l'intubation rapide pour les enfants et les bébés est livre-poids /6, $\pm$ $\frac{1}{10}$ pour les variables. La dose intermittente optima de maintien est environ $\frac{1}{10}$ à $\frac{1}{5}$ de la dose d'intubation administrée toutes les 15 à 30 minutes. La dose totale de maintien maxima tolérée pour les enfants semble être égale à la dose d'intubation et chez les bébés elle n'est que la moitié de la dose d'intubation.

5. Le degré et la durée de l'anesthésie au pentothal–curare et le relâchement chez les enfants sont comparables à ceux observés chez les adultes.

6. La quantité de pentothal–curare nécessaire pour le maintien peut être considérablement réduite par l'addition d'une quantité extrêmement petite (une trace) d'éther ou de trichloréthylène. Ceci s'est avéré particulièrement utile vers la fin des opérations, en vue d'une émergence rapide et pour réduire de moitié la dose totale de maintien de pentothal–curare dans les cas de longs procédés.

Pendant cette enquête tous les avantages bien connus de l'intubation rapide chez les adultes et le maintien au pentothal–curare–protoxyde d'azote ont été obtenus. Les désavantages et les dangers possibles pour les enfants sont facilement évités grâce à une sélection et une conduite intelligente et soignée de l'anesthésie.

Commentaires

A part l'échelle générale de dosages du pentothal–curare, les données et les observations dans le nombre limité de cas de cette enquête doivent être considérées comme étant préliminaires et provisoires jusqu'à ce que beaucoup plus de cas aient été rapportés, et préférablement par plusieurs chercheurs. Les proportions et l'étendue même de dosage exigeront peut-être une révision, particulièrement pour les petits bébés. En plus, diverses combinaisons d'autres relaxants et de barbituriques à courte action pourraient être étudées et servir comme anesthétiques en pédiatrie, et il se pourrait que chacun réponde plus exactement aux exigences particulières de cas spéciaux.

Les conditions préalables fondamentales pour l'emploi sûr de l'intubation rapide, et le maintien en anesthésie utilisant les relaxants barbituriques et le protoxyde d'azote chez les enfants et les bébés sont:

(*a*) Conduite de l'anesthésie par ceux-là seulement qui possèdent les connaissances, l'expérience et l'entraînement technique experts nécessaires pour parer à toutes les phases et les problèmes possibles.

(*b*) On commencera avec les enfants plus âgés et on descendra alors graduellement l'échelle poids-âge de pédiatrie à mesure qu'on gagnera de l'expérience.

(*c*) Une respiration assistée adéquatement ou mieux, contrôlée, sera instalée de l'injection rapide à l'émergence.

(*d*) Prendre soin d'éviter un dosage trop fort pour le maintien surtout dans le cas de longs procédés.

(*e*) Soins et observations experts et soignés après l'opération, dans une salle de recouvrance bien équippée ou son équivalent.

La négligence de ces conditions peut causer la mort, et on aura tendance à blâmer les agents inanimés eux-même plutôt que ceux qui sont responsables du soin et de l'administration de ces agents. On en trouve un exemple dans une revue statistique récente (3) où Beecher attribue aux relaxants musculaires le blâme pour les mortalités résultant de l'anesthésie. Griffith très adroitement indique en une phrase la vraie cause et la prévention de telles mortalités, "Si la revue de Beecher prouve quoi que ce soit, je crois qu'elle prouve que nous avons besoin d'un plus grand nombre d'anesthésistes, entraînés afin d'employer intelligemment et individuellement leurs connaissances et suivant les exigences les plus élevées de la bonne médecine." Les résultats de cette étude sont présentés dans cet esprit et dans l'espoir que les enfants ne continueront pas à payer le prix de la morbidité causée par l'éther pour la sécurité en anesthésie.

Addenda

Depuis la fin de cette enquête, la technique décrite a été employée dans plus de 400 cas d'enfants par le Dr. A. B. Noble de Kingston, Ontario, et dans un grand nombre de cas d'enfants par le Dr. H. M. Slater et ses collaborateurs à Montréal. Nous exprimons notre reconnaissance au Dr. Slater pour ses précieux conseils et critiques.

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CARDIO-PULMONARY DISTURBANCES IN THORACIC SURGERY

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DURING the last two years and a half, 243 thoracoplasties, 264 pulmonary resections, and 6 decortications were performed at Laval Hospital, Quebec. As anaesthetist, we observed various cardio-pulmonary disturbances during pre-, per-, and postoperative courses. We thought that the analysis of these problems could be highly interesting, and might provide some guidance when surgery is proposed for pulmonary tuberculosis.

During the preoperative period, complete evaluation of pulmonary function, cardiac reserves, and blood volume is imperative. Recent advances in the surgical treatment of diseases of the pulmonary and cardiovascular systems demand a deeper understanding of the function of these systems. Surgical treatment is being currently advocated for patients in whom respiratory and cardiac function are borderline. These patients' reserves should be fully and accurately evaluated before surgery. According to the classification of Baldwin, Pulmonary function studies may be divided into the mechanical or structural, and the alveolar respiratory or physico-chemical. Mechanical tests consider the lungs as bellows and the tests are either static in type (for vital capacity, inspiratory capacity, tidal air, expiratory reserve, residual capacity, total lung volume) or dynamic (for walking, ventilation, maximum breathing capacity, timed vital capacity). Alveolar respiratory tests are concerned with the quantity and quality of gaseous exchange at the inspiratory, alveolar, capillary, and tissue levels. They include tests for intra-pulmonary gas mixing, diffusion tests and arterial blood studies.

Until recently, we had to limit our activities to ventilation tests. We are now beginning alveolar exchange studies. Our studies on 220 patients would indicate that pulmonary tuberculosis reduces pulmonary efficiency. The actual vital capacity was found to be 75 per cent or less of the estimated vital capacity in 191 cases; 87 per cent. The actual maximum breathing capacity was found to be 75 per cent or less of the estimated maximum breathing capacity in 159 cases; 72 per cent.

For the evaluation of cardiac reserves, the venous pressure and circulation time are two very helpful tests. According to P. D. White, venous pressure is the criterion of the function of the right ventricle. Normal venous pressure ranges from 2 to 10 cm. of water. The critical level is 20 cm. of water. The clinical value of the circulation time is the estimation of the degree of decompensation in any heart case, especially left ventricular failure. The higher the figure expressing the circulation time, the greater is the degree of decompensation. Venous pressure was taken in 73 patients preoperatively. In 10 patients (14 per cent) venous pressure was found to be above 20 cm. H_2O; 48 patients (66 per cent) had more than 10 cm. H_2O; 15 patients (20 per cent) had a normal venous pressure. On the

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other hand, only 3 per cent of our patients showed a prolonged circulation time. We did electrocardiogram tracings on 199 patients. Of these, 160 had normal tracings; 12 patients showed right incomplete bundle branch blocks, which is not too significant; 6 patients had left axis deviation with left heart hypertrophy; 21 patients showed right axis deviation with strain. Most of the patients with right heart hypertrophy had severe pulmonary insufficiency.

Moot's test is an additional good criterion for estimation of cardiac reserves. This test multiplies the pulse pressure by 100 and the figure obtained is divided by the diastolic pressure. It was done on 73 patients: 30 patients had figures below 40 mm. Hg., the normal being between 40 and 60 mm. Hg.

It has been reported that tuberculous patients often show reduction of blood volume. Some clinical signs may help in this field but we like to rely on laboratory tests. The dye method using Evan's Blue or P.V.P. has appeared to us to be highly satisfactory. It was used for 65 of our patients. Twenty-four (24) patients showed a blood volume reduction of more than 600 cc.

In the light of all the above-mentioned studies, we have been able preoperatively to correct deficiencies and prevent complications as far as this was feasible. Pulmonary insufficiency was treated by respiratory exercises under the supervision of a trained physiotherapist. Patients were taught how to breathe and cough. Emphysematous patients were given positive pressure and aminophyllin which is mainly helpful when there is an elevation of the venous pressure. Bronchodilators like "Vaponefrin" given in aerosol may be indicated in obstructive endobronchial lesions. Blood volume was restored preoperatively to its normal value.

With a better knowledge of the patient's condition and following the correction of well-known deficiencies, the anaesthesia can be more safely begun. During the operative period, the anaesthetist comes up against the problem of anoxia. Anaesthetic agents are a matter of choice. On the other hand, adequate oxygenation of the patient is imperative. We have found that the prone position on the operating table seems to afford a better ventilation than the lateral position. This isolated measure would be inadequate. Endotracheal or endobronchial intubation permits one to deliver oxygen directly into the tracheobronchial tree under well-controlled conditions. Oxygen can be given under positive pressure which may prove to be very helpful if cardiac arrest occurs. Paradoxical breathing and mediastinal flutter are easily controlled. Free airways are at all times available; secretions can be quickly removed.

The ready removal of secretions is very important when dealing with tuberculous patients where bronchogenic spread may occur. For the surgeon who likes to operate in the lateral position, we favour the use of the Carlen's double lumen catheter. This tube completely separates the two lungs. It prevents flooding of the dependent good lung by secretions coming down from the diseased lung. It permits separate aspiration and inflation of each lung. In the prone position, there is good postural drainage of secretion which must come down the trachea as soon as it leaves the respective lung. A simple endotracheal tube permits good oxygenation without danger of spread. Yet the Carlen's double lumen catheter may also be helpful in the prone position. The bronchus to be sutured can be

completely isolated from the tracheobronchial tree. This enables the surgeon to close the bronchial stump under better conditions.

Very few of our patients showed respiratory acidosis. Preoperative and endoperative CO_2 combining power determinations revealed similar figures. There was an increase of 20 volumes per cent in 3.1 per cent of our cases and of 10 volumes per cent in 12 per cent of this series. In only one instance, we had a blood Ph at 7.3, at the end of the operation. Arterial oxygen saturation has been consistently normal. During the operation, blood lost is measured by the weighing of sponges and blood is replaced accordingly. This method has appeared to us to be satisfactory. Postoperative blood volume determinations closely correlated to the preoperative findings.

The thoracic operation is taking place in cardio-pulmonary zones which are the most reflexogenic of the body. Difficulties arising from vago-vagal reflexes are either of pulmonary or cardiovascular origin. They include bronchospasm with reduction of tidal air, apnea, a-v block, bradycardia, hypotension, arrythmia, tachy-arrythmia, cardiac asystole. They are more likely to occur in the presence of respiratory acidosis. Their prevention demands the following measures. Intubation must be performed after good topical anaesthesia of the vocal cords and with the patient in a fairly deep plane of general anaesthesia. Spreading of ribs stretches intercostal nerves and may induce the above-mentioned difficulties. We routinely block the intercostal nerves as soon as the muscles of the chest wall have been sectioned. We used long-acting agents that may by reducing pain benefit the patient postoperatively. Reflexes by traction on the pulmonary hilum may be reduced by infiltration of the vagus nerve with procaine or by the intravenous injection of atropine. Reflexes from pericardial manipulation may be minimized by the intrapericardial injection of procaine. Cardiac arrest is the ultimate effect of anoxia and marked reflex stimulation. If it occurs, the anaesthetist should immediately look for close co-operation with the surgeon and the surgical team. The surgeon immediately performs cardiac massage for adequate circulation. The anaesthetist gives oxygen under positive pressure. Intracardiac use of epinephrine may sometimes be helpful.

If ventricular fibrillation occurs, electric defibrillation should be performed. We have had 12 cases of cardiac arrest. They were all treated by oxygen under positive pressure, cardiac massages, and epinephrine intracardially. Six patients were successfully treated. Six patients did not recover cardiac activity and died.

During the immediate postoperative period of these patients, the anaesthetist is mainly concerned with removal of retained secretions and with the prevention of atelectasis. When the patient leaves the operating room, his tracheo-bronchial tree should be completely free of secretions. This freedom must be maintained throughout the postoperative course. Accumulation of secretions interferes with oxygenation by bronchial plugging and often leads to atelectasis, pneumonitis, or both. Excessive formation of secretions postoperatively can be avoided during the anaesthetic period itself by gentle handling of the tracheo-bronchial tree and by intermittent inflation of the operated lung. We advocate the use of less depressive sedatives like "Demerol," "Levo-dromoran," "Largactil." The patient must be encouraged to cough and breathe deeply. Aerosol may be helpful in mobilizing

secretions. Position is frequently changed. Intercostal nerve block with a long-acting agent is routinely performed. Alcohol solutions may be given intravenously. According to Dr. Mary Karp of the Wesley Memorial Hospital, Chicago, the need of narcotics is reduced to 30 to 50 per cent.

We tend to agree with Dr. Karp's opinion. If these measures fail to prevent retention of secretions or atelectasis, tracheo-bronchial aspiration must be immediately performed. Transnasal aspiration may be tried. Broncho-aspiration is often needed. Tracheotomy is sometimes indicated.

Right heart failure sometimes occurs postoperatively. This is to be expected in respiratory borderline patients and in the aged group of patients. The anaesthetist must be well aware of this complication. The slightest doubt demands the help of a cardiologist.

We have stressed the definite importance of the preoperative evaluation of the thoracic surgical patient. We have also described methods of prevention and treatment of the more serious complications. Finally, extensive investigation and survey have been possible in 53 consecutive cases recently operated on. In this group of patients, we have had no deaths and no serious cardio-pulmonary disturbances. This work has been supported by a Public Health Research grant.

We strongly feel that the great majority of complications can be prevented with a better knowledge of the patient's condition and with proper anaesthetic techniques.

Résumé

Depuis deux ans et demi, 243 thoracoplasties, 264 résections pulmonaires et 6 décorticatations ont été pratiquées à l'Hôpital Laval de Québec. Comme anesthésiste, nous avons eu l'occasion d'observer différents troubles cardio-pulmonaires avant, pendant, et après ces interventions. Nous avons pensé qu'une analyse de ces problèmes serait d'un grand intérêt pour les phtysiologistes dans les cas de tuberculose pulmonaire où un traitement chirurgical est indiqué.

A la phase pré-opératoire, l'observation d'un nombre imposant d'opérés thoraciques démontre qu'il est impératif de bien évaluer la fonction pulmonaire, les réserves cardiaques et l'état du volume sanguin. A l'aide de ces connaissances, nous avons pu corriger certaines déficiences et à la fois nous étions prêts à solutionner tout problème survenant au cours d'anesthésie ou dans les suites post-opératoires.

A la période opératoire proprement dite, nous luttons contre l'anoxie en réalisant chez nos malades l'oxygénation la plus parfaite possible. Nous maintenons le volume sanguin en remplaçant adéquatement le sang perdu et nous combattons les accidents vagaux de l'anesthésie tant respiratoires que cardio-vasculaires par tous les moyens mis à notre disposition.

A la période post-opératoire, la rétention de sécrétions ou même l'atélectasie pulmonaire et la décompensation cardiaque sont les principales complications auxquelles l'anesthésiste doit s'attendre et nous vous présentons à la fois le traitement prophylatique et thérapeutique de ces deux grandes complications.

Nous avons démontré l'importance de l'évaluation pré-opératoire d'un patient en chirurgie thoracique. Nous avons aussi décrit les méthodes préventives et le

traitement des complications les plus sérieuses. Enfin, grâce à un octroi gouvernemental, nous avons pu faire des études cardio-respiratoires chez 53 cas consécutifs, de chirurgie thoracique et parmi ce groupe, nous n'avons enrégistré aucune mortalité et aucune complication cardio-respiratoire sérieuse.

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THE DETERMINATION OF ALVEOLAR CARBON DIOXIDE

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THE determination of alveolar CO_2 concentration depends on the measurement of the amount of CO_2 absorbed from a 20 ml. sample of alveolar air by a concentrated solution of NaOH. Pressures are equilibrated to atmospheric at the start and finish to eliminate false volume changes due to pressure differences. Temperature changes are insignificant because the procedure takes only a minute or less, and the apparatus does not change in temperature provided certain simple precautions are taken.

APPARATUS

This consists of a glass analysis chamber which can be easily assembled (see diagram). The lower stem (*a*) consists of a section of a 5ml. pipette, to measure 3 ml. graduated at $\frac{1}{10}$ ml. The zero mark should be a cm. or more from the lower end. This 3 ml. pipette is connected by rubber tubing (*b*) to a larger glass section (*c*) consisting of glass tubing of approximately 1 cm. inside diameter. A 2-inch length of rubber tubing (*d*) of relatively small bore (e.g., 5 mm.) is attached to the upper end and clamped in the middle (*e*). Both ends of the larger glass section are drawn out somewhat to permit connections to the rubber tubing without a shoulder. The section of larger glass is cut to such a length that the internal capacity of the whole chamber from the zero mark to the clamp is 20 ml., i.e., the larger section is of about 17 ml. capacity. This can be determined by filling the chamber from a 20 ml. syringe or burette, and adjusting to final volume by sliding the glass tube the proper distance into the rubber connector (*b*).

The chamber is washed with water to wet the inside and mounted vertically on a stand with a burette clamp with the lower end immersed in water *at room temperature* so that the inside meniscus is exactly at the zero mark. The immersion reservoir (*f*) should be deep enough to accept the total length of the 3 ml. pipette. (A tall beaker or short graduate is suitable.) The assembly is allowed to stand for a few minutes before use to allow drainage of excess water from the inside, and to allow the glass to attain room temperature.

PROCEDURE

The sample of alveolar air is collected in a small anaesthetic bag (*g*). This is attached to the upper end of the gas chamber by a glass connection. The bag is unclamped at the connector, the clamp (*e*) on the gas chamber is squeezed open though not removed. At the same time the sampling bag is squeezed so that the analysis chamber is flushed through several times and completely filled with the gas sample. The excess bubbles out of the lower end. When filled with the sample, clamp (*e*) is allowed to close, thus trapping the gas sample in the chamber with the meniscus at or near the tip of the measuring pipette and below the open surface of the water in the reservoir.

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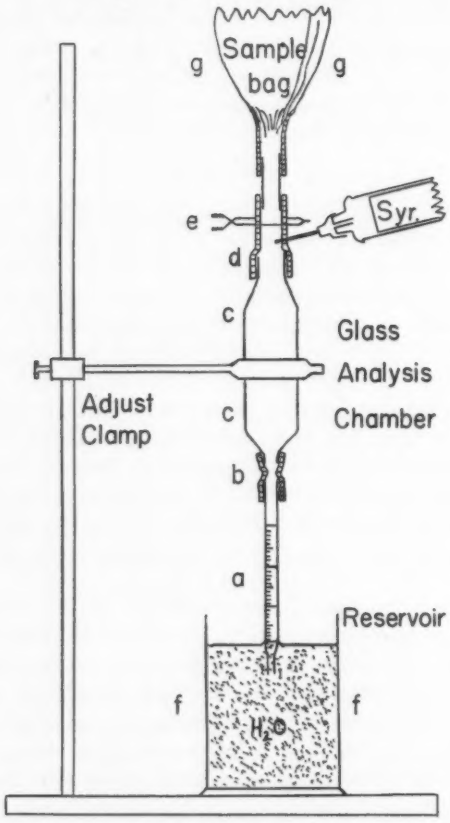
Owing to the handling of the sampling bag the entrapped sample will be warmer than room temperature, and will immediately start to cool and shrink, causing the meniscus to rise in the pipette. The meniscus will however become stable at a level below the zero mark as soon as the gas sample attains the same

FIGURE 1

Diagram of CO_2 Analyser



temperature as the glass chamber (which is room temperature).

Using a dry empty syringe and 25 gauge needle, gas is slowly withdrawn from the chamber by puncturing the rubber tubing (*d*) below clamp (*e*), until the inside meniscus is again at the zero mark on the pipette.

The analysis chamber thus contains exactly 20 ml. of gas sample at barometric pressure and room temperature.

Using a small syringe and 25 gauge needle, approximately ½ ml. (an excess) of a half-saturated solution of NaOH is slowly injected into the chamber through the rubber tubing (*d*). The needle is directed so as to allow the NaOH to flow down the inside wall of the chamber on opposite sides thus providing a large absorption surface. The excess trickles down into the pipette and collects at the

water surface. Care must be taken to inject the NaOH slowly to avoid an accumulation of it at the rubber connector (*b*) which might occlude the smaller bore of the pipette. The contained CO_2 will immediately start to be absorbed and the meniscus will rise in the pipette. When absorption is complete it will attain a constant level. The chamber is then lowered on the stand until the menisci inside the pipette and outside in the water tank are at the same level. The entrapped gas residue after CO_2 absorption is again at baromtric pressure and at room temperature.

The amount of CO_2 absorbed is the volume of the water now occupying the pipette from the zero mark (starting level) to the final reading of the meniscus. As the original alveolar sample was 20 ml., the per cent composition of CO_2 is obtained by multiplying the amount actually absorbed by 5. Example: amount actually absorbed, 1.1 ml.; per cent CO_2 composition of alveolar gas sample is 5.5.

The apparatus is thoroughly washed through with water following each test and again mounted in position for the next analysis. This allows time for the excess water to drain off, and for the glass to return to room temperature.

Precautions

The most serious potential errors are changes in volume which would occur if the temperature of the gas changed during the test. Such temperature changes are readily avoided if the glass is at room temperature throughout the test. Since the procedure is brief, there is insufficient time for fluctuations of room temperature to affect the temperature of the glass significantly. However, errors will occur if the glass was warmer or cooler than the room prior to the start of the test, and progressively cooled or warmed as it approached room temperature during the test. Progressive expansion of the gas due to warming of the chamber while absorption with NaOH was proceeding would offset the absorption and give low readings; progressive contraction of the gas due to cooling of the chamber would reduce the total gas volume and thus add to the shrinkage due to absorption of CO_2, and give high readings.

Therefore, the chamber should not be moved from one position to another (e.g., from a sunny or cold window, or from a position near a radiator to a more remote position) unless time is allowed for the glass to attain the air temperature of the new position. Similarly, the glass should not be handled immediately prior to, or during, a test, or washed with hot or cold water.

To avoid these possible errors the apparatus should preferably be used in a sheltered place in the room against an inside wall, and washed from a tank of water which has been standing for some time, and is, therefore, already at room temperature. The chamber should also be handled at the burette clamp rather than by grasping the glass in the hand.

Depending on the fineness of the $\frac{1}{10}$ ml. graduations of the pipette, readings can be made accurately to one-half division or better, i.e., 0.05 ml., giving an accuracy of approximately 0.25 per cent CO_2 concentration. This is adequate for most clinical work, and is probably less than the sampling error. Concentrations of CO_2 up to 15 per cent can be determined.

This technique is easily mastered, and is suitable for CO_2 determinations on

a hospital ward. The apparatus can be assembled cheaply from supplies available in standard laboratories. Its chief merit is the rapidity with which CO_2 determinations can be made.*

The Collection of Alveolar Air Samples for CO_2 Analysis

The greatest source of error in attempting to determine the alveolar CO_2 concentration lies in (*a*) the difficulty of obtaining true alveolar air samples; (*b*) the possibility that, because the respiratory rhythm may be altered when the subject gives the sample, CO_2 may accumulate in, or be blown off from, the alveoli just prior to the sampling. The alveolar CO_2 concentration would thus not be the proper value for the patient at that time.

The first possible sampling error requires that care be taken to collect an expired sample only after the air in the dead space is expelled. Since the dead space gas amounts to approximately 130 ml. and is low in CO_2, contamination of the sample by gas collected early in expiration will cause low readings. Only the latter ½ or ⅓ of the expired volume should be collected.

If the patient has a tracheotomy and is in a respirator this is easy. By watching the neck seal of the respirator (or some other part that moves in accordance with the pressure changes), one can easily learn to make quick contact between the nipple of the sampling bag and the tracheotomy tube at approximately mid-point of expiration. By opening a spring clip on the bag at the same time, samples can be collected from a series of expirations until the bag is filled.

If the patient has not got a tracheotomy the technique is more difficult and one has to obtain co-operation through practice, using a mouthpiece (or mask). Alternatively, a Haldane tube, or similar divice can be used.

It should always be remembered that a rubber anaesthetic bag, even when empty and collapsed, usually contains considerable gas either from the atmosphere or from a previous sample. This residue will dilute the first sample taken from the next subject.

Therefore, the bag should first be filled with a preliminary sample from the subject, and then emptied. This will wash out almost all the original residue of gas in the bag. A second collection from the patient will then be undiluted by gas from extraneous sources.

Recognizing its potential errors, the author much prefers bag sampling of alveolar air obtained by accumulating the tidal end-displacement of several expirations, rather than analysis of a single end-sample. The flexibility of the bag is also preferred to rigid devices, such as a syringe or pump.

When the sample is to be obtained from patients breathing on their own the technique of collecting end-samples without changing the respiratory rhythm can usually only be developed with practice. Some time spent on this with the patient will usually result in a significant improvement in the constancy of results. The greatest variation occurs in patients who try too hard to help, and are not relaxed, or who are too ill to co-operate.**

*An alternative method for free CO_2 analysis has also been developed which is "dry" and employs no solutions. It is portable, even quicker to carry out than the above method, and accurate to 0.1 per cent composition of CO_2 in the sample. Arrangements for manufacture of the apparatus are being made.

**The problem of sampling errors is considered to be so important that much time has been

LA DETERMINATION DU DIOXIDE DE CARBONE ALVEOLAIRE

HAROLD V. RICE, M.D., PH.D.

LA détermination de la concentration du CO_2 alvéolaire dépend de la mesure de la quantité de CO_2 absorbé par une solution concentrée de NaOH à partir d'un échantillon de 20 cc. d'air alvéolaire. Les pressions sont équilibrées à la pression athmosphérique au début et à la fin pour éliminer les changements erronés de volumes dus aux différences de pression. Les changements de température étant minimes, l'opération prend au maximum une minute et la température de l'appareil ne change pas, pourvu que certaines précautions élémentaires soient prises.

APPAREIL

Il consiste en une chambre d'analyse en verre qui s'assemble aisément (voir diagramme). La tige inférieure (*a*) se compose d'une section de pipette de 5 cc. calculée pour mesurer 3 cc. et graduée au $\frac{1}{10}$ de ml. Le point zéro doit se trouver à un centimètre ou plus de l'extrémité inférieure. Cette pipette de 3 cc. est reliée par un tube de caoutchouc (*b*) à une section de verre plus large (*c*) consistant en un tube de verre d'environ 1 cm. de diamètre intérieur. Un tube de caoutchouc long de deux pouces (*d*) et d'un diamètre intérieur relativement petit (par exemple 5 mm.) est attaché à la partie supérieure et pris dans une pince en son milieu (*e*). Les deux extrémités de la section de verre la plus large sont étirées quelque peu de manière à permettre les raccords sans soutien avec les tubes de caoutchouc. La section de verre la plus large est coupée à une longueur telle que la capacité intérieure de l'ensemble de la chambre à partir du point zéro jusqu'à la pince soit de 20 ml., c'est à dire que la capacité de la section la plus large soit d'environ 17 ml. On peut déterminer cela en remplissant la chambre à partir d'une seringue ou burette de 20 ml., en réglant le volume final et en faisant glisser le tube de verre dans le raccord de caoutchouc.

On lave la chambre avec de l'eau pour mouiller l'intérieur et on la monte verticalement sur un support à burettes en immergeant l'extrémité inférieure dans de l'eau *à la température environnante* de manière à ce que le ménisque intérieur soit exactement au point zéro. Le réservoir d'immersion (*f*) doit être assez profond pour recevoir la longueur totale de la pipette de 3 ml. (Un grand bécher ou un petit verre gradué convienne.) On attendra quelques minutes avant d'employer l'appareil pour permettre le drainage de l'eau en surplus à l'intérieur et pour permettre au verre d'atteindre la température environnante.

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spent in developing a device through which the patient simply breathes and which automatically rejects the first portion of the expired volume, and collects the latter portion. The amount rejected can be adjusted to the size of the patient. The patient is not required to control his respiratory movements in any manner during the sampling. He is required only to breathe casually and naturally through the apparatus, which is so designed as to provide minimal resistance, dead-space, etc.

While relatively simple, this automatic alveolar air sampler requires some machining in its construction. Its assembly is, therefore, not practical in a routine laboratory. Investigations into the possibility of having it manufactured are now in progress.

Opération

L'échantillon d'air alvéolaire est receuilli dans un petit ballon à anesthésie (*g*). Celui-ci est attaché à l'extrémité supérieure de la chambre à gaz par un raccord de verre. On relâche la pince du ballon au niveau du raccord et la pince (*e*) de la chambre à gaz est ouverte, mais non retirée. Au même instant, le ballon échantillon est comprimé de telle sorte que la chambre d'analyse soit purgée à plusieurs reprises et complètement remplie du gaz échantillon. L'excès barbotte à la sortie inférieure. Lorsque le plein est achevé, la pince (*e*) est refermée, emprisonnant ainsi l'échantillon de gaz dans la chambre, avec le ménisque au niveau de ou près de la pointe de la pipette à mesurer et au dessous de la surface libre de l'eau du réservoir.

Par suite de la manipulation du ballon échantillon, l'échantillon emprisonné sera plus chaud que la température environnante, et commencera immédiatement à refroidir et à se contracter, causant une élévation du ménisque dans la pipette. Le ménisque se stabilisera cependant au dessous du point zéro aussitôt que l'échantillon de gaz atteindra la même température que la chambre de verre (qui est la température environnante).

A l'aide d'une seringue vide et sèche et d'une aiguille de calibre 25, on retire lentement le gaz en ponctionnant le tube de caoutchouc (*d*) au dessous de la pince (*e*), jusqu'à ce que le ménisque intérieur atteigne à nouveau le point zéro sur la pipette.

La chambre d'analyse contient ainsi exactement 20 cc. d'échantillon de gaz à la pression barométrique et à la température environnant.

A l'aide d'une petite seringue et d'une aiguille de calibre 25, on injecte lentement dans la chambre au travers du tube de caoutchouc (*d*) environ ½ cc. (excès) d'une solution de NaOH à demi saturée. On dirige l'aiguille de manière à permettre au NaOH de couler le long de la paroi intérieure de la chambre sur les deux côtés opposés, offrant ainsi une grande surface d'absorption. L'excès coule goutte à goutte dans la pipette et se ramasse à la surface de l'eau. Il faut veiller à injecter le NaOH doucement pour éviter qu'il ne s'accumule au niveau du raccord de caoutchouc (*b*) et n'obstrue ainsi le plus petit diamètre intérieur de la pipette. Le CO_2 qui se trouve à l'intérieur commencera immédiatement à être absorbé et le ménisque montera dans la pipette. Quand l'absorption sera complète, il atteindra un niveau constant. On abaisse ensuite la chambre sur le support jusqu'à ce que les ménisques à l'intérieur de la pipette et à l'extérieur dans le réservoir à eau soient au même niveau. Le résidu du gaz emprisonné, après absorption du CO_2, est à nouveau à la pression barométrique et à la température environnante.

La quantité de CO_2 absorbé est le volume de l'eau qui occupe maintenant la pipette depuis le point zéro (niveau de départ) jusqu'à la dernière lecture du ménisque. Comme l'échantillon alvéolaire original était de 20 ml., la composition de CO_2 (en pourcentage) s'obtient en multipliant par 5 la quantité effectivement absorbée. Exemple : quantité effectivement absorbée, 1,1 ml. ; teneur (pourcentage) en CO_2 de l'échantillon de gaz alvéolaire : 5,5.

Après chaque test, on lave soigneusement l'appareil avec de l'eau et on le remonte pour l'analyse suivante. Ceci permet à l'excès d'eau de s'écouler et au verre de revenir à la température environnante.

Précautions

Les erreurs possibles les plus sérieuses sont les changements de volume qui se produisent si la température du gaz change pendant l'expérience. Ces changements de température s'évitent facilement si le verre reste à la température environnante pendant tout le test. L'opération étant courte, les fluctuations de la température environnante n'ont pas le temps d'affecter sensiblement la température du verre. Cependant des erreurs se produiront si le verre était plus chaud ou plus froid que la salle avant le début de l'expérience, et s'il s'est progressivement réchauffé ou refroidi jusqu'à approcher de la température environnante pendant l'expérience. Une dilatation progressive du gaz due à l'échauffement de la chambre pendant l'absorption par NaOH compenserait l'absorption et donnerait des lectures trop basses : une contraction progressive du gaz due au refroidissement de la chambre réduirait le volume total du gaz et accroîtrait ainsi la contraction due à l'absorption de CO_2, et donnerait des lectures trop élevées.

Par conséquent, on ne doit pas déplacer la chambre (par exemple, d'une fenêtre ensoleillée ou froide, ou d'une position près d'un radiateur à une position plus éloignée) à moins qu'on ne laisse au verre le temps d'atteindre la température environnante dans sa nouvelle position. De même, le verre ne doit pas être manipulé juste avant, ou pendant, une expérience, ni lavé avec de l'eau chaude ou froide.

Pour éviter ces erreurs possibles, l'appareil sera employé de préférence dans un endroit abrité le la salle, contre une paroi intérieure, et lavé dans un réservoir d'eau qui aura été placé dans la salle quelque temps auparavant et se trouve donc déjà à la température environnante. La chambre devrait aussi être manipulée au niveau de la pince à burettes plutôt qu'en prenant le verre dans la main.

Suivant la finesse des graduations au $\frac{1}{10}$ de cc. de la pipette, on peut faire avec exactitude des lectures à une demi-division près c'est-à-dire 0.05 cc., ou plus précises, indiquant la concentration en CO_2 avec une exactitude d'environ 0.25 pour cent. Ceci convient pour la plupart des travaux cliniques et reste sans doute au dessous de l'erreur d'échantillonage. Des concentrations en CO_2 s'élevant jusqu'à 15 pour cent peuvent être déterminées.

Cette technique se possède facilement et convient aux déterminations de CO_2 dans les salles d'hôpital. L'appareil peut être monté à peu de frais à partir d'éléments disponibles dans les laboratoires standard. Son principal mérite est la rapidité avec laquelle on peut effectuer les déterminations en CO_2.*

La Récolte des échantillons d'air alvéolaire pour l'analyse de CO_2

La majeure source d'erreurs, quand on tente de déterminer la concentration du CO_2 alvéolaire, réside dans (*a*) la difficulté d'obtenir de véritables échantillons d'air alvéolaire; (*b*) l'éventualité que, parce que le rythme respiratoire du sujet peut être altéré quand il donne l'échantillon, CO_2 puisse s'accumuler dans, ou être expulsé des alvéoles juste avant l'échantillonage. La concentration du CO_2 alvéolaire ne serait pas, dans ce cas, la teneur réelle pour le patient à ce moment.

*Une autre méthode pour l'analyse de CO_2 libre a été également mise au point : cette méthode est « sèche » et n'exige pas de solutions. Elle est portative, plus rapide que la méthode ci-dessus, et plus précise jusqu'à une teneur en CO_2 de 1 pour cent dans l'échantillon. Des arrangements pour la fabrication de l'appareil sont en cours.

La première possibilité d'erreur d'échantillonage exige qu'on veille à ne recueillir un échantillon qu'après éjection de l'air dans les espaces nuisibles. Le gaz des espaces nuisibles s'élevant à environ 130 cc. et sa teneur en CO_2 étant faible, la contamination de l'échantillon par du gaz recueilli prématurément pendant l'expiration provoquera des lectures trop basses. La moitié ou le tiers seulement du volume expiré devrait être recueilli.

Si le patient n'a pas de trachéotomie, la technique est plus difficile et il faut l'opération est aisée. En regardant le collet du poumon d'acier au cou (ou toute autre partie qui se déplace suivant les variations de pression), on peut facilement apprendre à établir un contact rapide entre le mamelon du ballon-échantillon et le tube à trachéotomie environ au milieu de l'expiration. En ouvrant une pince à ressort sur le ballon an même instant, on peut recueillir des échantillons d'une série d'expirations jusqu'à remplissage du ballon.

Si le patient n'ax pas de trachéotomie, la technique est plus difficile et il faut obtenir la coopération du malade par la pratique et l'emploi d'un tampon ou masque. On peut également employer un tube de Haldane ou autre appareil du même genre.

On se souviendra toujours qu'un ballon à anesthésie en caoutchouc, même s'il est vide et dégonflé, contient d'habitude une quantité considérable de gaz provenant soit de l'athmosphère soit d'un échantillon antérieur. Ce résidu diluera le premier échantillon pris sur le sujet suivant.

En conséquence, le ballon devra toujours être rempli d'un échantillon préliminaire du sujet, puis vidé. Cette opération évacuera presque complètement le gaz résiduel contenu dans le ballon. Un deuxième prélèvement effectué sur le patient ne sera pas alors dilué par des gaz d'origine étrangère.

Tout en admettant ses chances d'erreurs, l'auteur préfère de beaucoup l'échantillonage de l'air alvéolaire dans un ballon, obtenu en accumulant l'air courant provenant de la dernière partie de plusieurs expirations, à l'analyse d'un unique échantillon de fin d'expiration.

Il préfère aussi la flexibilité du ballon aux dispositifs rigides, tels que seringues et pompes.

Quand il s'agit d'obtenir un échantillon sur des patients qui respirent d'eux-mêmes, la technique de prélever des échantillons de fin de respiration sans changer le rythme respiratoire ne peut d'habitude être mise au point que par la pratique. Quelques instants passés avec le malade dans ce but se traduiront d'habitude par une nette amélioration dans la constance des résultats. Les variations les plus importantes se produisent chez les malades qui font trop d'efforts pour aider, et ne sont pas détendus, ou qui sont trop malades pour apporter leur concours.*

*Le problème des erreurs d'échantillonage est considéré comme si important qu'on a passé beaucoup de temps à mettre au point un dispositif dans lequel le malade se borne à souffler ce qui rejette automatiquement la première partie du volume expiré, et recueille la dernière portion. La quantité rejetée peut être réglée suivant la taille du malade. La malade n'est pas obligé de maitriser ses mouvements respiratoires en aucune façon pendant l'échantillonage. On lui demande seulement de respirer normalement et naturellement à travers l'appareil qui est conçu de manière à offrir une résistance, et un espace nuisible, moindre.

Quoique relativement simple, cet échantilloneur automatique d'air alvéolaire demande quelque usinage dans sa construction. Son montage n'est donc pas pratique dans un laboratoire ordinaire. Une enquête quant à la possibilité de le faire fabriquer est en cours.

ANAESTHESIA FOR EYE SURGERY

J. M. WISHART, M.D.*

SURGERY on the eye, except in children, has in the past been considered the field for topical or local (subconjunctival or retrobulbar) anaesthesia. At times, however, it has been necessary, because of an unco-operative patient, to use general anaesthesia. These occasions have been fraught with fear and apprehension both for the surgeon and for the anaesthetist. The end results have usually not been the best to be desired. On other occasions an anaesthetist has been asked to supervise a patient during the administration of curare as an adjuvant to topical anaesthesia. This technique also has not proven to be satisfactory.

As eye surgery has progressed, there have been many attempts to improve on the very necessary anaesthesia. These attempts have followed two main directions: one, to improve the topical anaesthesia and the other to devise ways and means of rendering the patient oblivious to the trials of surgery on the eye. This paper will deal only with the latter method, as it is felt that both the patient and the eye surgeon will be more appreciative of this new technique.

In reviewing the literature, we find that most eye surgeons have directed their attention to changing or increasing the basal narcosis and continuing with local anaesthesia. To this end, Johnson (1) has proposed the use of a combination of morphine, hyoscine, and ephedrine as premedication to render the patient semi-conscious. Moner (2) suggests the use of intravenous barbiturate, demerol, or morphine to keep the patient quiet during surgery under topical anaesthesia. He also advocates the use of curare to produce akinesia and a reputedly relaxed patient. In many of these cases an anaesthetist was required to administer oxygen.

Kilgore (3) describes the use of pentothal combined with local anaesthesia. He reports, however, that frequently a specialist anaesthetist is required to give a gaseous anaesthetic by way of an endotracheal tube. In 300 cases he reports no untoward effects referable to the general anaesthesia. Sanders and Cutler (4) advocate the use of a specially designed pharyngeal airway with a balloon-type fitting. This airway is to be used with pentothal, nitrous oxide, and cyclopropane. In their series no curare was used.

Parrish, Eason, and Karp (5) advance opinions very similar to our own on this subject. They state that endotracheal anaesthesia may be undertaken almost routinely in eye surgery with minimum danger to the patient and gratifying results to the surgeon and anaesthetist. Thus we see a progressive trend toward the displacement of local anaesthesia by general anaesthesia for eye surgery.

GENERAL PRINCIPLES

With general anaesthesia the patient is relieved of all apprehension and nervous tension, and thus will accept the trials of surgery with equanimity. This is particularly appreciated after one operation under local anaesthesia. There is now no need to hold the eye steady, nor visualize the flashes of light associated

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with eye surgery. As a rule, too, the surgeon is more satisfied. He no longer needs to hurry and there is no fear of a sudden movement of the eye at a crucial moment. He does not need to concern himself with the general condition of the patient, as it is constantly supervised by the anaesthetist. Further, the centrally fixed eye with lowered intraocular pressure is easier to operate upon.

Technique

We have arrived at our present method by a series of trials and errors—fortunately none disastrous. We have used various combinations: pentothal with local anaesthesia; pentothal and nitrous oxide or cyclopropane or ether transported through a variety of oropharyngeal or nasopharyngeal airways. Each was discarded because of lack of control of the airway and the anaesthetic, or because sneezing, coughing, or laryngospasm increased our difficulties. With these methods, too, our surgeon was none too happy, as we frequently encroached on his sterile field.

As a result of this somewhat experimental work, we proceeded to a method using an endotracheal tube which gives complete control of the airway and the gaseous anaesthetic and keeps the anaesthetist away from the sterile field. The only restriction was on movement of the head in order to reduce irritation of the glottis.

Our patients are admitted the afternoon before surgery and are examined by the anaesthetist. Sodium amytal or chloral hydrate in appropriate doses are given as h.s. sedative. The preoperative sedative is given three-quarters of an hour before the time of operation and usually consists of seconal gr. ¾, demerol 35–50 mgm., hyoscine gr. 1/200 and a gravol suppository or largactil 25 mgm. This produces a basal narcosis and a basis for retrograde amnesia.

In the operating room the anaesthetic is begun with 250–400 mgm. of pentothal and 40 mgm. of succinylcholine, or 20 mgm. of succinylcholine and one mgm. of syncurine, or 20 mgm. of flaxedil. The larynx is then exposed with a laryngoscope and sprayed with 5–10 per cent cocaine or ½ per cent pontocaine, after which intubation is carried out. As a rule, neither pharyngeal packing nor a cuffed tube are used because of the high incidence of coughing on their removal. Inflation of the lungs is carried out by rhythmic pressure on the rebreathing bag until normal respiratory excursion returns. Cyclopropane, nitrous oxide, and pentothal are administered as required to maintain the depth of anaesthesia in light third stage throughout the operation and until the dressings are on, tracheal toilet completed, and the tube out. This helps to prevent coughing while the tube is in place or after its removal, which might cause loss of vitreous. Oxygen is continued by mask until the respirations are well established and the condition of the patient is considered satisfactory for removal to the recovery room. Just prior to starting the operation, the surgeon does a facial nerve block on the appropriate side in order to prevent squeezing of the eyeball by the periorbital muscles and so loss of vitreous during or after the operation.

Postoperatively our patients are placed in the Simm's position with the operative side uppermost. Oxygen is given by mask for one hour to help prevent

coughing which occasionally follows removal of the tube. Gravol or largactil are administered to decrease nausea and vomiting. After recovery of consciousness the patient is encouraged to breathe deeply and move from side to side and is given general supportive care. Resyl tablets, to keep mucus in a more liquid state, help to prevent chest complications.

This technique has been used for all intraocular operations with very satisfactory results. All eye operations receive similar care, but the extraocular cases are not so exacting.

Anaesthesia for eye surgery in children is usually for extraocular procedures. For these cases we use seconal at bedtime and seconal, hyoscine, codeine, or demerol in appropriate dosage for premedication. Cyclopropane by mask serves for induction, and is continued via endotracheal tube for maintenance, supported by nitrous oxide or ether. On this regimen, the children arrive in the operating room asleep, making induction peaceful and smooth. They are kept somnolent for forty-eight hours postoperatively by frequent doses of barbiturate. This reduces fretting and pulling off of dressings, but does not interfere with the taking of feedings or movement in bed.

Complications

For the surgeon, the main fears with general anaesthesia are coughing during and after the anaesthetic and post-anaesthetic vomiting. The coughing is controlled by a reasonably deep plane of anaesthesia until the endotracheal tube is removed, and the administration of oxygen by mask in the immediate postoperative period. Nausea and vomiting are largely controlled by the use of gravol and largactil in the pre- and postoperative periods.

Hoarseness and sore throat as a result of intubation are minimal and have been greatly relieved by nuporals or aspergum. An active nursing régime of movement and deep breathing with administration of resyl tablets has prevented any chest complications even in known cases of chronic bronchitis or asthma.

One unexpected difficulty arose following some of our anaesthetics. A few patients became quite senile and fell out of bed or pulled off their dressings. One eye had to be removed after removal of a cataract as a result of this. However, we now cover only the eye on which surgery was performed and have had no further difficulty.

In our series of 242 operations on adults, 125 have been for cataract removal. The rest were for squints, iridenclysis, iridectomies, trephines, enucleations, etc. We have done 78 operations on children for squints. Of the 125 cataract operations we have lost only the one eye noted above. In all the rest the results have been quite satisfactory. Our patients have been completely unselected, ranging in age from 49 to 95 years, and with a variety of pre-existing diseases—hypertension, diabetes, bronchitis, previous coronary occlusion, etc. We alter our premedication to suit each case with respect to age and condition and, where it was deemed advisable, obtained the aid of a competent internist for special treatment. We have found that with adequate sedation these patients have amnesia and are pleased to have no recollection of the day of their operation.

Summary

1. We have presented a technique of general anaesthesia for eye surgery which is safe and pleasant for the patient and is satisfactory to the surgeon and anaesthetist.

2. Pentothal, a relaxant, and cyclopropane and nitrous oxide per endotracheal tube are considered a superior anaesthetic routine for any eye surgery.

3. Patients who have received general anaesthesia show no apprehension when they return for a second operation as is evident when this is to be done under local anaesthesia.

Résumé

Une série de cas et une technique d'anesthésie générale pour la chirurgie de l'oeil sont présentés. L'anesthésie générale est plus facile pour le patient, réduit la tension et les conditions d'urgence pour le chirurgien, et satisfait les exigencies de l'anesthésiste.

Nous avons employé le pentothal, un relaxant, l'anesthésie topique du larynx avec cocaïne ou pontocaïne, suivis de cyclopropane endo-trachéal et de protoxyde d'azote à une profondeur générale d'anesthésie au troisième degré.

Le seconal, le démerol et l'hyoscine servirent à la prémédication, le gravol ou le largactil étant ajoutés pour réduire les nausés et le vomissement. L'oxygène, le gravol et le largactil, constituant un régime actif de soins après l'opération, ont réduit au minimum la toux, la nausée, le vomissement et les complications pulmonaires.

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ANAESTHETIC DEATHS IN ALBERTA

E. A. Gain, B.A., M.D.*

In 1952 the Alberta Division of the Canadian Anaesthetist's Society decided that it would like to know the situation concerning anaesthesia in this province. As there were only approximately twenty certified trained anaesthetists at that time, a large proportion of anaesthetics must be administered by untrained individuals, mostly general practitioners. Therefore it was the feeling of the Alberta Division that hospital training in anaesthesia for the future general practitioner should be as compulsory as is training in medicine, surgery and obstetrics, before he is licensed to practise. Incorrect anaesthesia can be the most lethal of medical procedures. Therefore steps were taken to have established a committee to investigate deaths following anaesthesia and surgery.

In September, 1952, at the annual meeting of the Alberta Division of the Canadian Medical Association a committee was formed to study this matter and to report the results of its work. The committee commenced this study in January, 1953, reviewing the charts of all patients who died within thirty days of anaesthesia and surgery. In Alberta all such charts must by law be submitted to the Department of Public Health. The officers of this department kindly sent all of these charts to this committee.

The committee's purpose was to determine how well or how poorly anaesthesia and surgery were being performed in this province. No attempt was made to carry out an academic study of the many factors involved. A total of 168 charts were received. Attempts were made to obtain all possible information but rarely could any more information be obtained than was already in the case record. Anaesthetic records were almost always inadequate. The greatest single deficiency was in autopsy examinations which were performed in only 51.19 per cent of cases. As a result of this lack of information there were undoubtedly many more anaesthetic deaths and the figures which follow are conservative.

Of the 168 deaths there were 26 which were classified as preventable anaesthetic deaths, 46 as preventable surgical deaths, and 96 which were classified as inevitable fortuitous or unassessable. The latter classification was necessary because sufficient information could not be obtained to classify them in any other way.

The distribution according to the type of surgery is shown in Table I.

It will be noted that there were no anaesthetic deaths associated with thoracic and neurosurgical procedures. This may be owing, in part at least, to the fact that these procedures are usually done in larger centres by trained and well-equipped anaesthetists. The anaesthetic deaths are high in the ear, nose, and throat and other head and neck procedures. The cause was invariably some respiratory difficulty and none of these patients had an endotracheal anaesthesia.

*Edmonton, Alberta.

TABLE I

Operation	Anaesthetic death	Surgical death	Inevitable fortuitous deaths unassessable	Total
Ear–nose–throat	3	3	3	9
Other—head & neck	3	1	1	5
Thoracic	0	4	6	10
Gastric	3	6	5	14
Biliary	2	8	10	20
Small and large bowel	5	11	17	33
Hernia	4	1	3	8
Endoscopy	0	1	1	2
Orthopaedic	1	2	7	10
Obstetrical	1	0	4	5
Gynaecological	2	2	2	6
Neurosurgical	0	0	26	26
Others	2	7	11	20
	—	—	—	—
	26	46	96	168

Tables II and III help to disprove the widely held belief amongst practitioners that open ether is safe even in the hands of the inexperienced. Cyclopropane contributed the lowest incidence of deaths even though it is more often used in the poor-risk patient. This result is likely due to the fact that it is usually used by the trained and not the untrained anaesthetist.

TABLE II

NUMBER OF EACH ANAESTHETIC ADMINISTERED

Ether	Cyclopropane	Pentothal	Spinal	Spinal & Pentothal	Local	None	Total
42	25	27	20	23	17	14	168

TABLE III

ANAESTHETIC AGENTS ASSOCIATED WITH ANAESTHETIC DEATHS

Ether	Cyclopropane	Pentothal	Spinal	Spinal & Pentothal	Local	Total
9	2	7	3	4	1	26

Pentothal and spinal produced the results expected. Several of the cardiac arrests occurred with the combination of spinal plus pentothal. The one death with local was the result of procaine with epinephrine used in conjunction with self-administered trichloroethylene. This combination can be as dangerous as cyclopropane and epinephrine but unfortunately this fact is not generally known.

It will be noted that there is no mention of muscle relaxants. Relaxants were only used in 4 of the 26 cases, and in none of these 4 could the relaxant in the dose used and time administered have been responsible for the death.

TABLE IV

CAUSE OF DEATH IN 26 CASES CLASSIFIED AS ANAESTHETIC DEATHS

1. Anaesthetic overdose with respiratory and/or circulatory failure		10
2. Respiratory obstruction during anaesthesia		2
3. Respiratory obstruction following anaesthesia		3
4. Regurgitation or vomiting with aspiration		1
5. Convulsions during ether anaesthesia		1
6. Acute cardiac arrest, probably due to		
(*a*) Movement of the patient	2	
(*b*) Reflex disturbances with possible hypoxia and/or hypercarbia	3	
(*c*) Ventricular fibrillation due to drug incompatibility	1	
(*d*) Inadequate ventilation	3	9
		26

As expected and shown in Table IV the cause of death was most often associated with some respiratory derangement. Acute cardiac arrest is included as most cases were believed to be the result of the anaesthetic. The cause of this complication is of course often difficult to discover but is usually an improperly administered anaesthetic. Of these 9 cardiac arrests only 2 of the patients were in the older age group, none involved intrathoracic surgery, and only one was a poor risk. Therefore the committee felt justified in assigning their deaths to the anaesthetic.

Out of the 168 cases, 75 involved certified anaesthetists, 79 non-certified or general practitioner anaesthetists. In the remaining 14 cases the patient did not have an anaesthetic.

Of the 26 anaesthetic deaths, 8 involved certified anaesthetists and 18 non-certified anaesthetists. Unfortunately it proved impossible to obtain figures giving the total numbers of anaesthetics administered and operations performed in this province in 1953. Nor could figures for the number of anaesthetics administered by certified and non-certified anaesthetists be obtained.

As mentioned previously the purpose of this committee is to discover the true state of anaesthesia and surgery in Alberta, to decide what are the deficiencies, and what steps should be taken to correct them. The members of the Alberta Division of the Canadian Anaesthetists' Society have in the past few years attempted through the pages of the *Alberta Medical Bulletin* to give information concerning safety in anaesthesia to the general practitioners in this province. In addition, the author, at the request of the President of the Alberta Division of the Canadian Medical Association, is conducting a speaking tour of the district medical societies, attempting to point out and correct the errors which have been responsible for the anaesthetic deaths in this province.

The aim of this communication has been to show what the Alberta members are doing to improve anaesthesia in their province, and to solicit the support of the Canadian Anaesthetists' Society for their belief that clinical training in anaesthesia is as necessary as is clinical training in medicine, surgery and obstetrics, before the recent graduate is permitted to set forth into general practice, where in many areas he must because of necessity, often administer anaesthetics.

A PORTABLE SUCTION PUMP AND ITS USES

M. A. NICHOLSON, M.D., F.A.C.A.*

MECHANICAL suction apparatus is now standard equipment in most operating and recovery rooms for the use of the anaesthetist. During the last few years many elaborate mechanical respirators and resuscitators have been made available with attached suction. These have a wide range of usefulness but their costs may be prohibitive for general use and their operation may require specialized mechanical and technical knowledge, as well as the medical personnel familiar with the pathology of the respiratory disturbance. Constant supervision and co-operative services overload budgets and, if not in frequent use, equipment may be out of order when urgently needed. Power failures, mechanical defects, non-available electric outlets, or insufficient units give a wide range of usefulness for a simple suction pump operated by hand. The illustrated photograph provides such a piece of equipment. The construction is a large-size tire pump with a reversed valve. Surgical rubber tubing connects it with an ordinary throat suction bottle with a catheter tip that can be adapted to a metal or rubber tip. The end is mounted on a hardwood base. It is sturdy, easily transported, and can be dismantled quickly for cleansing and sterilization. The total weight is about 5 lb. Pumping against a closed system pressure is reduced to 10 cm. of mercury in three or four strokes.

RANGE OF USEFULNESS

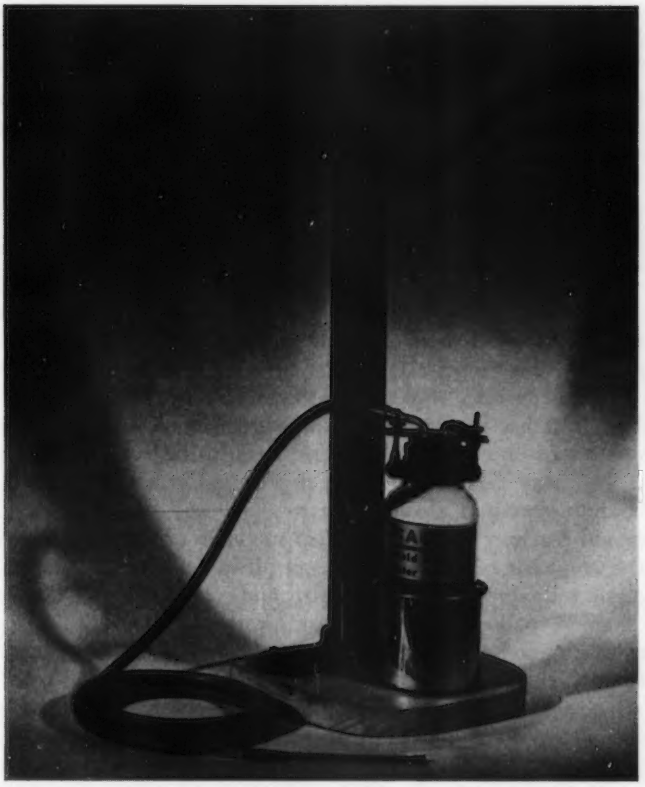
The apparatus serves as an auxiliary for the usual routines in surgery and obstetrical theatres, i.e., the removal of secretions from unconscious patients when medication is inadequate or improperly timed and balanced; or when unexpected vomitus, blood, or pus floods the respiratory tract; also, in head injuries and surgery of the head and respiratory tract. It can be used for resuscitation of the newborn.

Many diagnostic procedures are now carried out in dressing rooms or X-ray departments away from usual motor suction. The use of endoscopic instruments, orthopaedic manipulations, or the setting of fractures require brief anaesthesia. Psychiatrists frequently use intravenous barbiturates for shock therapy or diagnosis. Anaesthesia for any of these may occasionally produce an unexpected laryngospasm with various degrees of anoxia that may damage brain cells or be fatal if not readily corrected. Available suction, endotracheal tubes, and an oxygen mask provide good protection for the simplest procedures involving the use of anaesthetic agents, as well as for the treatment of medical or surgical patients in coma if secretions are obstructing the airway.

The medical uses of a practical suction apparatus are multiple. The larynx has been well termed the "death zone" by Chevalier Jackson with the epiglottis the "watch dog." The anatomical and physiological variations at different age levels, the variations in balance of central and autonomic nervous systems, and

*Saskatoon, Saskatchewan.

FIGURE 1



variable responses to the multitude of drugs and their combinations can produce unpredictable situations. "Just a little pentothal" for a supposedly minor procedure may be a hazardous experience for patient and physician, and remind us how futile it is to be over-specialized in clinical medicine. Many systemic diseases including the familiar chronic respiratory infections result in coughing or impairment of swallowing. The acute infections include the obscure virus diseases (poliomyelitis being the most familar), tetanus, and diphtheria; the many chronic degenerative lesions or new growths in the central nervous system impair muscle tone, and normal secretions accumulating in the throat crevices may be a source of infection to the respiratory tract—a source of reflex irritation, a mechanical obstruction in the airway, or a combination of all three.

Many of these cases require long-term nursing, and terminal care involves some method of assisting patients to rid themselves of irritating secretions. The bedside nurse is often more aware of this than the physician. Prophylactic suction can conserve much of the patient's reserve and often helps to temporize in the harrowing decision of an elective rather than an emergency tracheotomy.

A small portable motor suction may be noisy and unavailable, and a simple available one may give the nurse and apprehensive patient assurance and prevent additional fatigue and distress. Many patients can endure much discomfort, but panic at the irritation of a nasal feeding tube which may encroach on the airway and set up trigger reflexes in the larynx. Throat suction can decrease the amount of sedation that further depresses the respiratory centre. The statisticians confront us with an increasingly large number of older people. This provides us with a changing picture of illness and will mean more nursing care for cerebral accidents, degenerative lesions, and malignancies. A recent survey reports that in Saskatchewan, one of Canada's younger provinces, the number of persons over 65 increased from 3.4 per cent to 8 per cent between 1931 and 1951.

Emergency Uses

Distinctions between civilian and military casualties decrease. Modern living involves exposure to violence. "It is safer for a woman to have a baby than to cross the street in traffic," was a recent comment by a well-known American obstetrician. Motor car accidents involve pedestrians of all age groups. Injuries to occupants tend to involve the head and neck, to pedestrians fractures of the extremities. All may have respiratory depression and obstruction. Increased usage of barbiturates and alcohol add to diagnostic problems of patients in coma. First-aid teaching stresses technical methods of artificial respiration and neglects the emphasis of a non-obstructed airway before mechanical aids are used. This unit resembles a fire extinguisher and could be a unit in safety equipment for firemen, policemen, and first-aid workers.

The unit was made for the writer in the workshop of the Anaesthesia Department at Charity Hospital, Louisiana, a few months ago. A full-time mechanic who had a special interest in medical equipment helped to make this Department unique. Here many simple aids were improvised for polio patients according to individual needs. A suction similar to this model was made and installed in the station wagon of a young man with a permanent tracheotomy. This enabled him to spend weekends at home or attend a drive-in theatre.

Appreciation is expressed to Dr. John Adriani and various departments of Charity Hospital for many courtesies extended to me, and to Mr. G. A. Morgavi, who assembled the portable suction pump.

Summary

A simple and economical portable suction pump is described, which is suitable for hospital, first-aid, or home-nursing use. Its operation is simple and contrasts with much elaborate and costly equipment which is rarely used.

Résumé

Une pompe portative *simple* à suction et peu dispendieuse est décrite. Elle répond aux besoins de l'hôpital et du "nursing" à la maison et peut servir à administrer les premiers soins aux blessés. Cette pompe emploie une pompe à automobile dont les clapets sont inversés. L'assemblage est illustré dans le schéma. L'opération de la pompe est simple et offre un contraste à l'équipement compliqué et coûteux dont on se sert rarement.

MEETINGS

CANADIAN ANAESTHETISTS' SOCIETY COUNCIL—March 6, 1955

The annual winter meeting of the Council of the Canadian Anaesthetists' Society will be held in the Board Room, Medical Arts Building, Toronto, at 10:00 A.M. on Sunday, March 6, 1955.

CANADIAN ANAESTHETISTS' SOCIETY, WESTERN REGIONAL MEETING, Regina, Saskatchewan

The date for this meeting is to be announced. The programme of this meeting will be directed particularly to the General Practitioner Anaesthetist.

CANADIAN ANAESTHETISTS' SOCIETY, ANNUAL MEETING, Toronto—June 20, 21, 22, 1955

The programme for this meeting is nearing completion, and will be published in the April issue of the JOURNAL.

SECTIONS OF ANAESTHESIA, BRITISH MEDICAL ASSOCIATION and CANADIAN MEDICAL ASSOCIATION, Toronto—June 23, 24, 1955

WORLD CONGRESS OF ANAESTHESIOLOGISTS, Scheveningen, Holland—September 5–10, 1955

Correspondence should be addressed to Mr. W. A. Fentener van Vlissingen, Executive Manager, World Congress of Anaesthesiologists, Bilthoven, Holland. The congress fee will be 35 Dutch Guilders. It will be reduced for those who send in their application form before March 31, 1955 to 25 Dutch Guilders.

NEWS LETTER

Nova Scotia Division

The Nova Scotia Division were hosts for a Maritimes Regional meeting on November 3, 4 and 5, 1954. Guest speakers on this occasion were Dr. David M. Little of the New Haven Hospital, and the Department of Anesthesia of Yale University Medical School, New Haven, Connecticut, and Dr. R. A. Gordon of the Toronto General Hospital and the Department of Anaesthesia, University of Toronto.

* * *

Dr. R. W. M. Ballem, Dr. C. M. Kincaide, Dr. R. A. P. Fleming, and Dr. A. S. MacIntosh are associated in the group practice of anaesthesia in Halifax under the name "Central Anaesthesia Services."

* * *

New Brunswick Division

Dr. W. A. Oatway has returned from Montreal after completing the McGill Diploma Course. Doctor Oatway has been appointed Staff Anaesthetist at the Moncton Hospital, the Hôtel Dieu de l'Assumption, and the Moncton Tuberculosis Hospital.

* * *

Dr. J. Arthur Dobson has returned to Montreal to complete his training at the Children's Memorial Hospital. During the past two years, Dr. Dobson has been practising anaesthesia in Moncton.

* * *

Quebec Division

La Société d'Anesthésie de Québec held its first monthly meeting for the new year on Tuesday, October 5. Papers were presented by Dr. Lucien Rinfret and Dr. Simon Dombrowski. Titles of the papers were: "Venous Pressures with regard to Bleeding in Operative Patients" and "Comparative Results in Different Types of Respirators." Both papers were delivered in French.

At the business meeting, the following executive officers were elected for the coming year:

President	:	Dr. William Martin
1st. Vice-President	:	Dr. Roland Duchesne
2nd. Vice-President	:	Dr. Irene Lapierre
Secretary-Treasurer	:	Dr. Adeline Comeau
Directors	:	Dr. Eugene Allard (retiring president)
	:	Dr. Gaston Comtois
	:	Dr. Paul Plourde
	:	Dr. Lucien Rinfret
	:	Dr. Paul Galibois

Ontario Division

Dr. Virginia Apgar, New York City, was guest speaker at a staff meeting of the Department of Anaesthesia of the Women's College Hospital, Toronto, on November 1, 1954.

* * *

Dr. John Blair, recently Resident Anaesthetist at the Toronto General Hospital, is now practising anaesthesia at the Northwestern General Hospital, Toronto.

* * *

Dr. Doreen Caplin, recently Resident Anaesthetist at the Hospital for Sick Children, Toronto, has been appointed to the staff of Mount Sinai Hospital, Toronto.

* * *

Dr. H. I. Axelrod has been appointed to the staff of Mount Sinai Hospital, Toronto, on the completion of the postgraduate course in Anaesthesia at the University of Toronto.

* * *

Dr. Garnet Dixon, formerly of the staff in anaesthesia of the Toronto East General and Orthopaedic Hospital, has been appointed to the staff of the Toronto Western Hospital.

* * *

Dr. Charles Crompton has been appointed to the staff of the Toronto Western Hospital on completion of the postgraduate course in Anaesthesia of the University of Toronto.

* * *

Saskatchewan Division

Dr. Gordon Wyant has taken up his duties as Professor of Anaesthesia at the University of Saskatchewan in Saskatoon.

* * *

A Western Regional meeting is being held in Regina in March, 1955, under the auspices of the Saskatchewan Division. The programme of this meeting will be directed particularly to the General Practitioner Anaesthetist.

* * *

Alberta Division

The annual business meeting of the Alberta Division was held at the Palliser Hotel, Calgary, on September 28. Of particular interest was the first report of the Committee for the Study of Anaesthetic and Operating-Room Deaths. This committee, consisting of an anaesthetist, a pathologist, and a surgeon, was formed two years ago by the Alberta Division of the Canadian Medical Association on the request of the Alberta Division of the Canadian Anaesthetists' Society. The committee has now completed the review of anaesthetic and operating-room deaths for its first full year of operation, from February, 1953, to February, 1954, and has submitted its first comprehensive report to the Alberta Division of the Canadian Medical Association. This report has been studied by the Alberta

Division of the Canadian Anaesthetists' Society. Under its terms of reference this committee studies the chart of every patient who dies during or following anaesthesia and surgery within a period of seventy-two hours, and, where necessary, seeks fuller information from the physician concerned.

* * *

The September meeting of the Edmonton Anaesthetists' Society was held on September 23, at the Garrison Officers' Club, in Edmonton. The Executive elected for the coming year, 1954–55, is as follows:

Chairman: Dr. Nelson Nix, succeeding Dr. Dave Moffatt
Secretary: Dr. Joseph Scales, succeeding Dr. George Moonie

* * *

Dr. Abel Morales Orive, President of the Fifth Mexican Congress of Anaesthesiology, in forwarding the programme for that Congress (November 14–20, 1954) extended official greetings to the Canadian Anaesthetists' Society. Unfortunately, this programme was received too late for publication in the JOURNAL before the date of the Congress.

* * *

Dr. Charles Stewart, Montreal, Dr. H. J. Shields and Dr. C. H. Robson, Toronto, Dr. D. Aikenhead, Burlington, and Dr. J. Blezard, London, Ontario attended the meeting of the American Academy of Anesthesiologists in Cincinnati in October, 1954.

* * *

Dr. Harry Slater, Montreal, was the official representative of the Canadian Anaesthetists' Society at the Congress of the Brazilian Society of Anaesthesioligists in September, 1954.

BOOK REVIEWS

SPINAL EPIDURAL ANALGESIA by P. R. Bromage. E. & S. Livingstone Limited (Macmillan Company of Canada Limited). Price $2.50.

This is a well illustrated volume dealing with all facets of Epidural Anaesthesia. The sections dealing with the anatomy of the epidural space, the technical details of the method, and indications and contra-indications for its use are particularly well done. Not all readers will accept without reservation many of the statements made in the discussion of Physiology, and the discussion on the drugs to be used must be considered as reflecting the author's personal opinion. Altogether, however, the reader will find this a very useful monograph on the subject.

R. A. G.

MODERN PRACTICE IN ANAESTHESIA, Edited by Frankis T. Evans. Second edition, Butterworth & Co. (Canada) Limited. Price $13.00.

The second edition of this excellent book includes three new chapters as well as changes in the manner of presentation of several other topics. Although there are sixty additional pages, the number of chapters is less, owing to the rearrangement of some of the subjects.

The group of eminent contributors has been joined by Drs. Sheila Anderson, D. M. Carnegie, John Gillies, Cecil Gray, C. F. Scurr, and David Slome, all of whom have penned authoritative articles in their several fields.

The conciseness and clarity with which the authors have given their information and described their clinical methods enable the reader to understand and enjoy the book and to copy the methods if desired. This should prove a useful book in any anaesthetist's library.

S. A. F.

PHARMACOLOGY by M. G. Mulinos and C. C. Lieb. Second edition, Oxford University Press. Price $7.00.

Dr. Mulinos first wrote his Pharmacology in 1944, and this second edition has been published to include new material. The original aim of the Outline has been retained: "to present a concise yet complete exposition, in outline form, of the science of pharmacology, designed to bring the practitioner of medicine up to date in this complex and rapidly growing field."

This was an interesting book to read intermittently, but this reader found the interminable tabulation of information into sections A, B, C, 1, 2, 3, a, b, c, and so on, irritating, and, when examined carefully, there seemed to be nothing gained by it in many places. Attention was directed to the chapters of interest to anaesthetists. There was a great deal of pharmacological information given about analgesics, anaesthetics, and supportive drugs, but the writer did not give the impression that he was personally acquainted with the use of many of them. An initial dose of curare was said to be 60 mg. with supplementary doses of 30 mg., which the majority of anaesthetists would surely question. In the section on spinal anaesthesia "a solution containing epinephrine" was advocated for

subarachnoid injection, whereas we have been under the impression that the method has been considered unsafe by many anaesthetists. His statement that "as an anaesthetic, ethylene is superior both to ether and nitrous oxide" was certainly a bold one.

There was much material which seemed extraneous in a pharmacological book in other sections to which reference was made, and an insufficiency of the information sought.

S. A. F.

ANESTHESIOLOGY by forty American authors, DONALD E. HALE, M.D., Editor. Philadelphia: F. A. Davis Co. (Toronto: Ryerson Press), 1954. Pp. 772. Price $16.50.

This voluminous work which took several years to produce is, as is described in the preface, a symposium on the basic sciences and practice of anaesthesia in all its aspects by a group of the most illustrious teachers of anaesthesia on the American continent. The list of authors contains the names of several Canadians and former Canadians.

It would be impossible in a brief review to cover the various chapters. The pages are set up in double-column form which makes for faster reading, but increases the amount of paper required, and thus the weight of the book. Some chapters are liberally supplied with tables, illustrations, and references, whereas others are deficient in these aids. The chapter on Conduction Anaesthesia is well illustrated to show location and distribution of nerves, and the author has simplified the instruction by describing a single technique for each procedure.

In addition to chapters usually found in older text books there are also splendid chapters on Control of Pain, Resuscitation, Inhalation Therapy, Blood and Blood Substitutes, Anaesthesia Records, and Explosions and Fire Hazards. Unfortunately in this first edition there are no references to Hypotensive and Hypothermia techniques.

For the practicing anaesthetist, the teacher, and the student, this book will be most useful, and the Editor is to be congratulated on bringing together such a galaxy of well-known Authors.

S. M. C.

OPERATIVE SURGERY by ALEXANDER MILES and JAMES LEARMONTH. Oxford University Press. Price $6.00.

This practical surgical text from the Edinburgh school contains an introductory chapter on the Choice of Anaesthetic, by John Gillies, Reader in Anaesthetics, University of Edinburgh. The importance of the subject is indicated by the editors, by placing it first in the book. Premedication, and choice of anaesthetic, intravenous, volatile, and gaseous, with their limitations from a surgical standpoint, are covered. Cyclopropane is the anaesthetic of choice by the author, in major surgery. The problems of respiratory and circulatory failure in relation to surgery are mentioned. The author points out that "the benefits of modern anaesthesia must not be neutralized by prolonged surgical procedures." This chapter is meant for surgeons but its clarity and conciseness are noteworthy, and it is recommended to anaesthetists.

S.L.V.

APPOINTMENTS AVAILABLE FOR POSTGRADUATE TRAINING IN ANAESTHESIA IN CANADIAN HOSPITALS APPROVED BY THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

THE following information is derived from a survey recently conducted by the Canadian Anaesthetists' Society, and is published as provided by the hospitals and university departments concerned. It will be noted that the titles designating appointments of various grades vary from hospital to hospital. Specifically, the term *Resident* in some centres indicates a senior house appointment, available only after considerable training in Anaesthesia, while in other centres and individual hospitals it is a term applied to all postgraduate internes-in-training. The terminology used in each case below is that in use by the hospital or university in question, and the exact nature of each appointment must be deduced by reference to the qualifications required for it.

NOVA SCOTIA

1. DALHOUSIE UNIVERSITY, HALIFAX

Teaching Hospitals—VICTORIA GENERAL HOSPITAL
HALIFAX TUBERCULOSIS HOSPITAL
CHILDREN'S HOSPITAL, HALIFAX

Appointments	Number	Duration	Available 1955	Remuneration	Requirements
Resident in Anaesthesia	4	2–3 yrs.	3	1st yr—$50.00/mo. 2nd yr—$75.00/mo. 3rd yr—$75.00/mo. —— with full maintenance	Graduate of Class A Medical School Yearly appointments Applicants must forward full personal particulars and recommendations

Basic science training—Provided through the departments of Physiology, Pharmacology, Anatomy, and Pulmonary Investigation of Dalhousie University. Weekly lectures by staff and others. Research Fellows and Demonstrators in Basic Sciences by direct arrangement with the University.

Address applications to

Dr. Carl Stoddard,
Professor of Anaesthesia, Dalhousie University,
c/o Victoria General Hospital,
Halifax, Nova Scotia.

NEW BRUNSWICK

SAINT JOHN GENERAL HOSPITAL, SAINT JOHN

Appointments	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	12 mos.	1	$50.00 per mo.	Rotating interneship
Resident Anaesthetist	1	12 mos.	1	$150.00 per mo.	Previous training in anaesthesia

Basic science training—Didactic Lectures will be presented by Staff Members.

Address applications to

Dr. Carl R. Trask, M.D., D.P.H.,
Director,
Saint John General Hospital,
Saint John, New Brunswick.

QUEBEC

1. Laval University, Quebec

Teaching Hospitals—Hôtel-Dieu de Québec
Laval Hospital, Ste Foy, Québec

(a) Hôtel-Dieu de Québec

Appointments	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	5	1–4 yrs.	None	$100.00 to $300.00 per month	M.D. Senior interneship

Basic science training—100 hours theory per year: Anatomy, physiology, biochemistry, pharmacology, physics, pathology, laboratory (blood grouping, Rh, cross-matching).

Address applications to

Dr. Fernando Hudon,
Professor of Anaesthesia,
Laval University,
c/o Hôtel-Dieu Hospital,
Quebec.

(b) Laval Hospital, Ste Foy

Appointments	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	2	1 yr.	None	$100.00 to $150.00 per month	Some experience in general anaesthesia and interest in thoracic anaesthesia

Address applications to

Dr. Alphonse L'Espérance,
Superintendent,
Laval Hospital,
Ste. Foy,
Quebec.

2. Hôpital de l'Enfant-Jésus, Quebec City

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	1 year	1	$100.00/mo.	One year rotating interneship
Resident Anaesthetist	2	1 year	2	$200.00/mo.	One year senior interneship
Clinical Assistant	2	1 year	2	$300.00/mo.	One year residency in anaesthesia

Basic science training—Theoretical courses given once a week. Teaching is in French.

Address applications to

Eugene Allard, M.D.,
Chief, Dept. of Anaesthesia,
Hôpital de l'Enfant-Jésus,
Quebec City.

3. HÔPITAL ST. FRANCIS D'ASSISE, QUEBEC CITY

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	2	3 years	1	$100.00/mo.	Rotating interneship
Clinical Assistant	2	Full time	—	—	—

Basic science training—Anatomy, Physiology, Chemistry and Physics of Anaesthesia, Pharmacology. Three hours weekly from September to June. Teaching in French and English.

Address applications to

Roland Duchesne, M.D.,
Director of Anaesthesia,
Hôpital St. Francis d'Assise,
Quebec City.

4. MCGILL UNIVERSITY, MONTREAL

Teaching Hospitals—MONTREAL GENERAL HOSPITAL
ROYAL VICTORIA HOSPITAL, MONTREAL
MONTREAL NEUROLOGICAL INSTITUTE
CHILDREN'S MEMORIAL HOSPITAL, MONTREAL
ST. MARY'S HOSPITAL, MONTREAL
QUEEN MARY VETERAN'S HOSPITAL, MONTREAL
QUEEN ELIZABETH HOSPITAL, MONTREAL
REDDY MEMORIAL HOSPITAL, MONTREAL
ROYAL EDWARD LAURENTIAN HOSPITAL, MONTREAL

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident in Anaesthesia	36	3 yrs.	Some July 1	1st yr—$50.00/mo. 2nd yr—$100.00/mo. 3rd yr—$200.00/mo. plus full maintenance	Rotating interneship

The course is three years, leading to a Diploma in Anaesthesia from McGill University. Students are assigned for clinical residency to the co-operating hospitals on a six-month rotation basis.

Basic science training—Organized courses in Anatomy, Physiology, Biochemistry, and Pharmacology are conducted by the various University Departments. Two-hour Seminars are held two evenings a week throughout the teaching session of thirty weeks.
Fees payable to McGill University—Basic Science Course—$155.00
Annual Registration Fee—$10.00

Address applications to

H. R. Griffith, M.D.,
Professor and Chairman,
Department of Anaesthesia,
McGill University,
Montreal 2, Quebec.

5. UNIVERSITÉ DE MONTRÉAL, MONTRÉAL

Teaching Hospitals—HÔTEL-DIEU DE MONTRÉAL
HÔPITAL NOTRE-DAME, MONTRÉAL

(a) HÔTEL-DIEU DE MONTRÉAL

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	3	1 year	3	$200.00/mo.	Not specified
Resident Anaesthetist	1	2 years	1	$250.00/mo.	
Clinical Assistant	1	3 years	1	$600.00/mo.	
Clinical Fellow	6	full time	—	$10,000.00 to $18,000.00 per annum	
Other (unspecified)	1	6 mos.	—	$6,000.00	

Basic science training—Anatomy, Physiology, Pharmacology, and Biochemistry given by the postgraduate Diploma Course, University of Montreal.

Address applications to

Dr. Leon Longtin,
Hôtel-Dieu Hospital,
Pine Avenue,
Montreal, Quebec.

(b) HÔPITAL NOTRE-DAME, MONTRÉAL

Details of appointments—Not specified.
Basic science training—Postgraduate Diploma Course, University of Montreal.

Address applications to

Dr. Louis Lamoureux,
Directeur du Service d'Anesthésie,
Hôpital Notre-Dame,
Montreal, Quebec.

ONTARIO

1. UNIVERSITY OF TORONTO, TORONTO
Department of Anaesthesia

Teaching Hospitals—TORONTO GENERAL HOSPITAL
TORONTO WESTERN HOSPITAL
ST. MICHAEL'S HOSPITAL, TORONTO
HOSPITAL FOR SICK CHILDREN, TORONTO
TORONTO EAST GENERAL AND ORTHOPAEDIC HOSPITAL
WOMEN'S COLLEGE HOSPITAL, TORONTO
HAMILTON GENERAL HOSPITAL, HAMILTON
SUNNYBROOK HOSPITAL (D.V.A.)

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	15	2 years	9	$50.00, $75.00* and $125.00/mo. plus maintenance	1. Qualification registrable to practise medicine in Ontario. 2. One year rotating intern
Resident Anaesthetist	2	1 year	2	$100.00/mo. basic plus maintenance	As above plus 2 years' training in Anaesthesia in a recognized teaching centre
Clinical Fellow	1	8 mos.	1	$200.00/mo.	3 years' anaesthesia training or 2 years' anaesthesia plus 1 year in a basic science
Research Fellow	1	1 year	1	$200.00/mo.	2 years in anaesthesia with preferably 1 yr. in a basic science

*Remuneration for Senior Interns varies from hospital to hospital. Senior Interns are rotated at 3 month or 6 month periods within the hospital group to equate both experience and remuneration.

Basic science training—

Anatomy—32 lecture-demonstrations by Department of Anatomy.
Pathology—1 lecture weekly by Department of Pathology—Sept. to May.
Physiology, Pharmacology, Pathological Chemistry, Medicine and Anaesthesia—in syllabus of lectures covering 2 years.
Seminars and Hospital Anaesthetic Staff Meetings once weekly.

Address applications to

Dr. S. M. Campbell,
Associate Professor and Head of Dept. of Anaesthesia,
University of Toronto,
Toronto 5.

2. QUEEN'S UNIVERSITY, KINGSTON
Department of Anaesthesia
Teaching Hospitals—KINGSTON GENERAL HOSPITAL
HÔTEL-DIEU HOSPITAL, KINGSTON

(a) KINGSTON GENERAL HOSPITAL

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	1 year	1	$100.00/mo. and according to previous experience	One year rotation interneship

Address applications to
W. A. Campbell, M.D.,
c/o Kingston General Hospital,
Kingston, Ontario.

(b) HÔTEL-DIEU HOSPITAL

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	1 year	1	$125.00/mo.	One year rotation interneship

Basic science training—Weekly seminars include basic science subjects. Applicants are encouraged to accept part-time appointments in basic science departments if available.

Address applications to
A. B. Noble, M.D.,
Department of Anaesthesia,
Hôtel-Dieu Hospital,
Kingston, Ontario.

3. UNIVERSITY OF WESTERN ONTARIO, LONDON
Teaching Hospitals—VICTORIA HOSPITAL, LONDON
WESTMINSTER HOSPITAL, LONDON (D.V.A.)

(a) VICTORIA HOSPITAL

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	1 year	1	$125.00/mo.	Rotation interneship
Resident Anaesthetist	1	1 or 2 yr.	1	$150.00/mo.	Rotation and senior interneship
Clinical Fellow	1	1 year	—	Private fees	Senior interneship and residency of 3 years with acceptance by Royal College of Physicians & Surgeons for certification examination in 1 year

VICTORIA HOSPITAL (*Continued*)

Basic science training—The Senior Intern spends part-time in the Department of Pharmacology (Research and Demonstration) with added stipend from certain grants. The Resident spends part-time in Department of Physiology and Biochemistry (Research, Teaching & Demonstration) with added stipend from certain grants.

Address applications to

Dr. C. Kirk,
Superintendent, Victoria Hospital,
London, Ontario.

(b) WESTMINSTER HOSPITAL (D.V.A.)

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Assistant Resident	1	1 year	1	$2700.00 per annum	Two years' previous training

Basic science training—Available through University of Western Ontario.

Address applications to

Dr. W. D. S. Cross,
Chairman, Interne Committee,
Westminster Hospital,
London, Ontario.

4. OTTAWA CIVIC HOSPITAL, OTTAWA

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	2	1 year	—	$100.00/mo.	Junior rotating interneship

Basic science training—No specific planned basic science work in connection with anaesthesia. Full programme of postgraduate activities and basic science lectures available at the hospital and at Ottawa University.

Address applications to

Superintendent,
Ottawa Civic Hospital,
Carling Avenue,
Ottawa, Canada.

5. St. Joseph's Hospital, Toronto

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	1	1 year	0	$2700.00/annum	

Basic science training—Instruction from staff members each morning. Lecture weekly.

Address applications to

Dr. C. E. Tipping,
1 Brentwood Road North,
Toronto 18, Ontario.

6. Hamilton General Hospital, Hamilton

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	1 year	1	$150.00/mo.	Junior rotating interneship
Resident Anaesthetist	1	1 year	1	$225.00/mo.	Must have completed at least one year of a university post-graduate course in Anaesthesia

Clinical Anaesthesia only.

Address applications to

Dr. J. B. Neilson,
Superintendent,
Hamilton General Hospital,
Hamilton, Ontario.

7. St. Joseph's Hospital, Hamilton

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	4 mo.	1	$100.00/mo.	
Resident Anaesthetist	1	1 year	1	$200.00/mo.	(1) One year approved interneship (2) L.M.C.C.

Basic science training—One hour basic study and one hour Journal Reviews weekly.

Address applications to

Karl Kraft, M.D.,
St. Joseph's Hospital,
Hamilton, Ontario.

MANITOBA

1. Winnipeg General Hospital, Winnipeg

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	4				
Resident	2				
Senior Resident	1	Not specified	Not specified	Not specified	Not specified
Clinical Fellow	1				

Basic science training—Manitoba Medical College

Address applications to

Dr. Donalda Huggins,
Department of Anaesthesia,
Winnipeg General Hospital,
Winnipeg, Manitoba.

2. St. Boniface Hospital, St. Boniface, Manitoba

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	2	2 years	2	$75.00/mo. 1st yr. after graduation $100.00/mo. 2nd yr. after graduation $150.00/mo. 3rd yr. after graduation, and maintenance	Degree in Medicine
Clinical Assistant	2	2 years	0	Varies with experience	Preparing for certification

Basic science training—Anatomy and Physiology postgraduate courses at Manitoba Medical College. Biochemistry and Pharmacology lectures by anaesthetic staff.

Address applications to

Dr. P. L'Heureux,
Medical Superintendent,
St. Boniface Hospital,
St. Boniface, Manitoba.

SASKATCHEWAN

REGINA GENERAL HOSPITAL, REGINA

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	1	12 mos.	1	$200.00/mo. residence and meals	1 year rotation interneship

Address applications to

Director of Medical Education,
Regina General Hospital,
Regina, Saskatchewan.

ALBERTA

1. UNIVERSITY OF ALBERTA, EDMONTON

Teaching Hospitals—UNIVERSITY HOSPITAL, EDMONTON
EDMONTON GENERAL HOSPITAL
ROYAL ALEXANDRA HOSPITAL, EDMONTON

(a) UNIVERSITY OF ALBERTA HOSPITAL, EDMONTON

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	3	1 year	3	$840.00/annum	1 year rotating interneship
Resident Anaesthetist	2	2 yrs.	2	$1,200.00/annum	1 year rotating interneship and 1 year senior interneship
Clinical Assistant	1	1 year	1	to be decided	Completed certification requirements
Clinical Fellow	1	1–2 yrs.	1	$3,000.00/annum	1 year rotating 1 year senior 2 years resident
Research Fellow	1	1 year	1	to be decided	1 year rotating interneship 1 year senior interneship

Basic science training—Lectures, Laboratory Demonstrations, Research Laboratory.

Address applications to

Interne Committee,
University Hospital,
Edmonton, Alberta.

(b) EDMONTON GENERAL HOSPITAL, EDMONTON

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	2	1 year	1	$100.00/mo.	Rotating interneship

Basic science training—Some theoretical instruction and required reading. Residents take second-year clinical work and basic science training at the University Hospital.

Address applications to

O. Stechishin, M.D.,
Department of Anaesthesia,
Edmonton General Hospital,
Edmonton, Alberta.

(c) ROYAL ALEXANDRA HOSPITAL, EDMONTON

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	1	6 mos.	1	$100.00/mo.	Junior interneship
Resident Anaesthetist	1	12 mos.	1	$125.00/mo.	Not specified
Clinical Assistant	2	12 mos.	Not specified	Not specified	Not specified

Basic science training—University of Alberta.

Address applications to

Dr. D. R. Easton,
Superintendent,
Royal Alexandra Hospital,
Edmonton, Alberta.

2. CALGARY GENERAL HOSPITAL, CALGARY

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	1	1 year	1	$150.00/mo.	1 year junior rotating interneship and preferably 1 year in postgraduate training in anaesthesia

Clinical anaesthesia only.

Address applications to

Administrator,
Calgary General Hospital,
Calgary, Alberta.

BRITISH COLUMBIA

1. UNIVERSITY OF BRITISH COLUMBIA, VANCOUVER

Teaching Hospitals—VANCOUVER GENERAL HOSPITAL
SHAUGHNESSY HOSPITAL (D.V.A.)
VANCOUVER GRACE HOSPITAL

(a) VANCOUVER GENERAL HOSPITAL

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Clinical Assistant	3	1 year	1	$140.00/mo.	General rotating interneship
Clinical Associate	3	1 year	nil	$185.00/mo.	1 yr. rotating interneship 1 yr. Anaesthesia
Resident Anaesthetist	1	1 year	nil	$210.00/mo.	1 yr. rotating interneship 1 yr. Anaesthesia 1 yr. Basic Science 1 yr. Medicine
Research Fellow	2	1 year	1	$200.00/mo.	1 yr. rotating interneship 1 yr. Anaesthesia (preferred)
Other (unspecified)	2	1 year	2	$185.00/mo.	1 yr. rotating interneship

Basic science training—Anatomy, Physiology, Pharmacology, Biochemistry and Pathology in conjunction with the teaching staff of the University of British Columbia Medical School.

Address applications to

Dr. H. B. Graves,
Associate Professor of Surgery,
Director of Anaesthesia,
Vancouver General Hospital,
Vancouver, British Columbia.

(b) SHAUGHNESSY HOSPITAL (D.V.A.), VANCOUVER

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Senior Intern	2	1 year	2	$175.00/mo.	12 mos. prior interneship
Resident Anaesthetist	1	1 year	1	$250.00/mo.	Prior training in anaesthesia

Basic science training—Provided by Department of Anaesthesia, University of British Columbia

Address applications to

Dr. K. S. Ritchie,
Superintendent,
Shaughnessy Hospital,
Vancouver, British Columbia.

2. ST. PAUL'S HOSPITAL, VANCOUVER

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Resident Anaesthetist	1	1 year	1	$200.00/mo.	1. Graduation from a Medical School approved by the College of Physicians and Surgeons of British Columbia 2. One year junior rotating interneship

Basic science training—Supplied by Department of Anaesthesiology, University of British Columbia.

Address applications to

Sister Marie Celina, Superior,
St. Paul's Hospital,
1081 Burrard Street,
Vancouver 1, B.C.

3. CREASE CLINIC AND PROVINCIAL MENTAL HOSPITAL, ESSONDALE

Appointment	Number	Duration	Available 1955	Remuneration	Requirements
Clinical Assistant and Research Fellow	1	1 year	1	to be determined	(1) 1 yr. senior rotation (2) 1 yr. Basic Science, Pharmacology or physiology preferred (3) 1 yr. clinical anaesthesia (2 yrs. preferred)

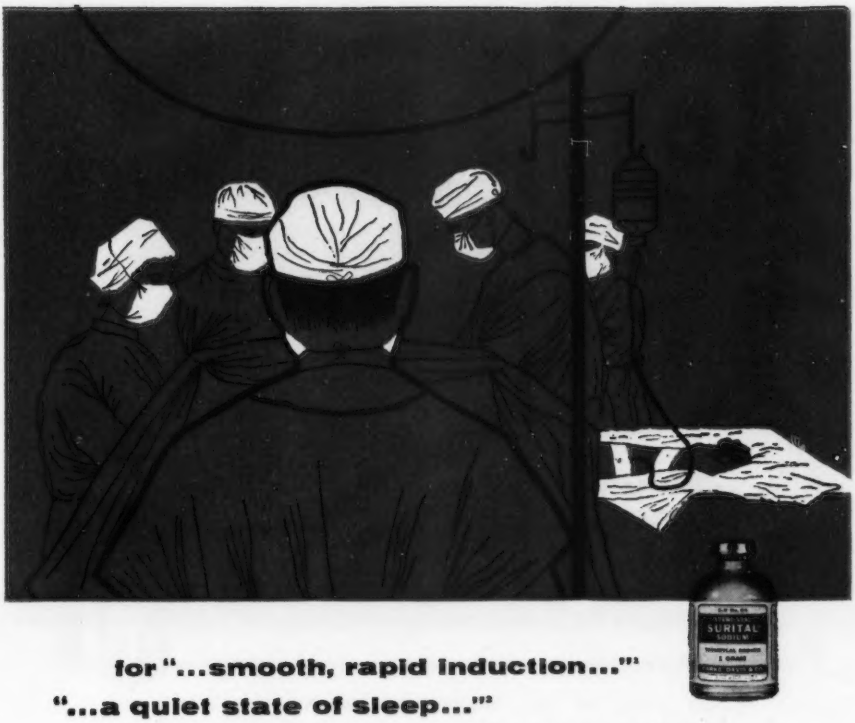
Address applications to

Dr. J. J. Carroll,
Director, Department of Anaesthesiology,
Crease Clinic and Provincial Mental Hospital,
Essondale, British Columbia.

4. ROYAL COLUMBIAN HOSPITAL, NEW WESTMINSTER

For details apply to

Dr. Bruce McEwen,
Director, Department of Anaesthesiology,
Royal Columbian Hospital,
New Westminster, British Columbia.



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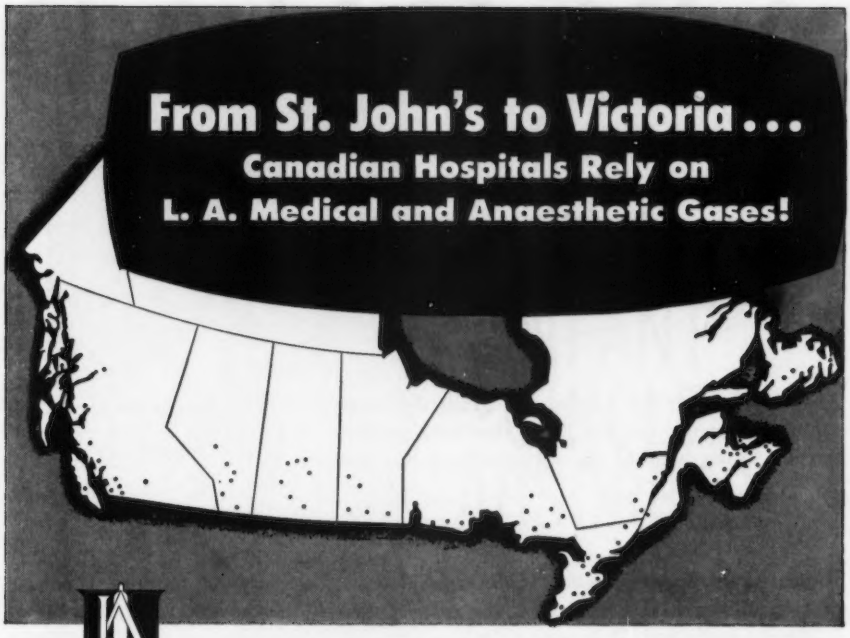
1. Helrich, M.; Papper, E. M., & Rovenstine, E. A.: *Anesthesiology* 11:33, 1950. 2. Stephen, C. R., & Martin, R.: *North Carolina M. J.* 12:501, 1951. 3. Phillips, H. S.: *Anesth. & Analg.* 32:56, 1953.



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[*]M.S. Sadove, G. M. Wyant, G. Gleave and P. C. Bucy, *J. Neurosurg.*, *11*:143, 1954.

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Manuscripts

Articles should be typewritten in double space on one side of the paper only. Pages must be serially numbered, and each page should carry at its head the name of the author and the title of the article in full or in an appropriate abbreviation. The article should be concluded by a summary which will be intelligible without reference to the main text. All articles should be accompanied by a résumé presenting the important features in short form, for translation into the French language. French-speaking authors should provide this résumé in the French language.

References to the literature should be clearly indicated in the text by arabic numerals in brackets, thus (4). They should be set out in numerical order at the end of the article, typed in double space, as follows:

4. Griffith, H. R. & Johnston, G. E. The Use of Curare in General Anaesthesia. Anesthesiology 3: 481 (1942).

References to books will state in order: Name of Author, Title of Book, Edition, Place of publication, Publisher, Year of Publication, such as:

Labat, G. Regional Anesthesia. 1st ed., Philadelphia: Saunders (1922).

The names of all authors will be given in the first instance in each reference. In further references to the same authors the abbreviated form "Griffith *et al.*" may be used.

Illustrations

Photographs should be unmounted glossy prints. Drawings and charts should be in black India ink on white paper. Reproductions in colour will be undertaken only at the expense of the author. All illustrations must be referred to in the text by Arabic Numerals (thus—Figure 3) the corresponding Arabic Numeral being clearly marked on the back of the illustration, together with the name of the author and the title of the article. Legends for illustrations must be typewritten in double space on a separate sheet of paper and clearly marked with the numerals corresponding to the appropriate illustrations.

Proofs

Galley proofs and engraver's proofs will be sent to the author and to the Editor for correction. A limited time will be allowed for return of proof from the Author, but in the event that Authors do not return proofs within the time allowed, the Editor may proceed to publish the article without awaiting return of proof from the Author.

Reprints

Authors' price list and order blank for reprints will be sent with galley proofs. Order for reprints must be returned with galley proofs to the Editor; otherwise reprints cannot be furnished at these prices.

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